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A Potential Role of the 5-HTTLPR Polymorphism in Self-Reported Executive Functioning

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Abstract. Intense effort is directed toward searching for associations between genes and neuropsychological measures of executive functions. In contrast, the impact of genetic polymorphisms on self-rating of everyday executive functioning has not been investigated so far. This study was designed to test associations of self-reported executive functioning, measured with the Behavior Rating Inventory of Executive Function (BRIEF-A), with dopaminergic and serotoninergic genes in non-clinical population and to assess impact of neuropsychological and personality characteristics on these associations. One hundred healthy adults completed the BRIEF-A, personality inventories SPQ-74, STAI, MMPI, and neuropsychological tests for executive functions. Polymorphisms in the *DRD4, COMT, DRD2, HTR2A*, and *SLC6A4* genes were genotyped. We revealed a significant main effect of the *SLC6A4*'s 5-HTTLPR polymorphism on BRIEF-A scores ($F = 2.21$, $P = .018$, $\eta^2 = .24$). Among the BRIEF-A measures, the genotype effect was significant for the Plan/Organize ($F = 7.34$, $P = .008$, $\eta^2 = .07$) and Task Monitor scales ($F = 4.33$, $P = .04$, $\eta^2 = .04$), and the Metacognition index ($F = 4.21$, $P = .043$, $\eta^2 = .04$). Carriers of the short allele reported fewer problems than homozygotes for the long allele. Correlations of the BRIEF-A measures with neuropsychological variables were weak, while those with personality characteristics were strong, with trait anxiety being the most powerful predictor of the BRIEF-A scores. However, the relationship between the 5-HTTLPR and BRIEF-A scores remained significant when trait anxiety was controlled for. The results suggest a potential role of the 5-HTTLPR in self-reported everyday task planning and monitoring.

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Executive functions (EF), also referred to as cognitive control, comprise processes that are necessary for goal-oriented behavior. They include at least three broad categories of basic executive processes: working memory/maintenance, response inhibition and cognitive flexibility, and higher-order EF (e.g., planning) built upon combinations of these three components (for review see Diamond, 2013; Etkin, Gyurak, & O'Hara, 2013). Most psychiatric disorders involve disruption of some aspects of EF (Eisenberg & Berman, 2010; Hosenbocus & Chahal, 2012; Roca, Vives, López-Navarro, García-Campayo, & Gili, 2015; Unoka & Richman, 2016). Furthermore, there is evidence that executive dysfunction may represent a potential core endophenotype of severe mental illnesses across traditional diagnostic categories (Etkin et al., 2013). Accordingly, intense effort is directed toward searching for associations between genes and neuropsychological measures of EF in both clinical and non-clinical populations (for reviews see Barnes, Dean, Nandam, O'Connell, & Bellgrove, 2011; Logue & Gould, 2014). At the same time, researchers have been questioning the sensitivity and ecological validity of neuropsychological EF variables (Rabin et al., 2006; Vriezen & Pigott, 2002). Based on the lack of significant relations between self-reported executive functioning in daily life and neuropsychological data, it has been suggested that the self-report measures may add unique information, over and above that obtained through traditional laboratory measures (Rabin et al., 2006). It is therefore of interest to examine whether specific genes contributing to variability of neuropsychological indicators of EF also influence subjective EF scores.

In an effort to integrate neuroscience and psychopathology, the U.S. National Institute of Mental Health developed the Research Domain Criteria (RDoC) framework (Cuthbert & Insel, 2013). It asks investigators to consider psychopathology in terms of maladaptive extremes along a continuum of normal functioning, focusing on basic dimensions of functioning (termed Constructs) instead of symptoms. The RDoC matrix provides constructs of interest along with promising units of their analysis including genes, molecules, cells, circuits, physiology, behavior, self-reports, and functional tasks. Within this framework, the *COMT, BDNF, DISC1, HTR2A, DRD2, DRD4, SLC6A4, CHRM4, DAT1*, and *MAO-A* genes were considered as candidates for the Cognitive Control construct, while the Behavior Rating

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Inventory of Executive Function (BRIEF), the most commonly used multifaceted rating scale for everyday EF assessment, was suggested as one of the self-report measures for this domain (NIMH, 2011). To our knowledge, the associations between the RDoC's candidate genes and the BRIEF have not been investigated so far.

The aim of the present study was to test the associations of an adult version of the inventory (BRIEF-A; Roth, Isquith, & Gioia, 2005) with RDoC's candidate loci for cognitive control in non-clinical population, with focus on dopaminergic and serotoninergic systems. The well-characterized functional polymorphisms in the *COMT, DRD2, DRD4, SLC6A4*, and *HTR2A* genes were investigated. The dopaminergic system has long been viewed as involved directly in executive functions. Though being contradictory, data suggest a potential role of the dopaminergic genes *DRD2, DRD4* and *COMT* in variability of different EF components, including performance monitoring, response inhibition, cognitive flexibility, and working memory (Barnes et al., 2011; Logue & Gould, 2014; Weiss et al., 2014). Serotonin (5-HT) also participates in neurotransmission in the prefrontal cortex and may influence EF. Accordingly, a variable number of tandem repeats (short [S] vs long [L]) in the promoter region of the serotonin transporter gene (5-HTTLPR) and functional variants in the *HTR2A* gene have been associated with EF in healthy individuals and psychiatric patients (Fallgatter et al., 2004; Holmes, Bogdan, & Pizzagalli, 2010; Lane et al., 2008; Weiss et al., 2014). It should be noted that the data for each gene are inconsistent as regard to relations with particular aspects of EF. Given this, we did not generate specific hypotheses and conducted an exploratory analysis of the associations between each gene and all BRIEF-A scales measuring different EF components.

In addition, we were interested in cognitive and personality variables that could mediate or modulate gene effects on BRIEF-A scores. On this account, relationships of BRIEF-A scores with neuropsychological indicators of EF and self-report measures reflecting a spectrum of psychological problems at the personality level were examined and statistically controlled for in the association analysis. Based on previous studies of older and clinical populations (Ciszewski, Francis, Mendella, Bissada, & Tasca, 2014; Garlinghouse, Roth, Isquith, Flashman, & Saykin, 2010; Rabin et al., 2006), we hypothesized that anxious or depressive mood rather than cognitive difficulties might impact experience of executive functioning problems in healthy individuals.

Method

Participants

Participants were 100 healthy adults of European ancestry (61% women) between 19 and 72 years of age (*M* 39.3; *SD* 13.3); 78% of them were university students or had higher education. Participants were recruited as part of a larger research on genetics of psychiatric disorders. In brief, subjects were sampled from the community by word of mouth. Each individual was asked about his/her psychiatric, neurologic or substance use history. Individuals who reported such conditions were not included into the sample. The entire research design required subjects to sign an informed consent for participation in the study, to donate blood samples for DNA extraction, and to complete a set of inventories. Subjects were also invited to attend a neuropsychological session. The research protocol was approved by the Mental Health Research Center's Ethic Committee.

For administrative and personal reasons not all inventories and tests were completed by each subject. Those subjects who completed the BRIEF-A among other inventories were included in the present study. Of them, 91 participants (age *M* 39.4; *SD* 12.7; 65% women) were also tested on a battery of neuropsychological tasks.

Assessment

The BRIEF-A is a 75-item questionnaire assessing executive functioning in daily life over the prior month. It includes nine clinical scales which generate two indices/factors, the Behavioral Regulation (BRI) and Metacognition (MI), and one summary composite, the Global Executive Composite (GEC). The BRI encompasses the Inhibit, Shift, Emotional Control, and Self-Monitor scales. The MI is composed of the Initiate, Working Memory, Plan/Organize, Task Monitor, and Organization of Materials scales. There are also three validity scales: Negativity, Inconsistency, and Infrequency. In the present study, no participants had elevated Negativity or Infrequency scales. The Inconsistency scale was elevated for three subjects. However, their BRIEF-A protocols showed no atypical response patterns and were retained for subsequent analyses. Standard T- scores were calculated for each of the clinical scales, indices, and for the summary composite. T-scores are based on data from a U.S. normative sample of 1050 adults and take into account respondent's age. Higher scores reflect poorer executive functioning.

To assess other psychological problems, 18 variables derived from Russian versions of the Schizotypal Personality Questionnaire (SPQ-74), State-Trait Anxiety Inventory (STAI), and Minnesota Multiphasic Personality Inventory (MMPI) were used. The SPQ-74 is a self-report measure modeled on DSM-III-R schizotypal personality disorder criteria (Raine, 1991). A total score as well as Interpersonal, Cognitive-Perceptual and

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Disorganized factors' scores were calculated for each subject. A 20-item scale from the STAI was used to assess trait anxiety (Spielberger & Gorsuch, 1983). A 377-item version of the MMPI (Berezin, Miroshnikov, & Rozhanets, 1976) yielded scores on three validity (L, F, and K) and 10 clinical scales including Hypochondriasis, Depression, Hysteria, Psychopathic Deviate, Masculinity/Femininity, Paranoia, Psychasthenia, Schizophrenia, Hypomania, and Social Introversion.

During the neuropsychological session a widely used tests of executive functioning, including the Semantic Verbal Fluency Test, Trail Making Test - Part B (TMT-B), Serial Subtractions, and Golden's Stroop Color and Word Test, were administered among others (for a review of neuropsychological tests see Diamond, 2013; Spreen, Strauss, & Sherman, 2006). The semantic fluency and TMT-B assess initiation and set-shifting (cognitive flexibility). In the semantic fluency task, subjects are required to generate words belonging to a designated category within 1 min. In the present study, "animals" and "fruits" were used and the sum of all admissible words was calculated. The TMT-B involves switching between connecting letters and numbers in their respective orders. The total time to complete the test was reported. The Serial Subtractions Test, which is a modification of the well-known mental tracking test "serial sevens", requires participants to count backwards out loud by twos and fives from two hundred. This version creates a considerable working memory load. The number of correct subtractions performed within 1 min was recorded. The Stroop Test assessing response inhibition included reading names of colors printed in black ink, naming colors of ink in which groups of letters "X" were printed, and naming colors of ink in which names of other colors were printed. A standard interference score was calculated.

Genotyping

DNA was extracted from blood samples using a phenol-chloroform method. The following polymorphisms were genotyped using previously described methods and primers: *DRD4* 48bp-VNTR and *COMT* Val158Met (rs4680) (Alfimova, Korovaitseva, Lezheiko, & Golimbet, 2014), *DRD2* Taq1A (rs1800497) (Monakhov, Golimbet, Abramova, Kaleda, & Karpov, 2008), *HTR2A* -1438 G/A (rs6311) (Golimbet, Alfimova, & Mityushina, 2004), *SLC6A4* 5-HTTLPR (Golimbet et al., 2010). For technical reasons different genotypes were available for different numbers of participants. The number of available genotypes for each polymorphism is presented in Table 1.

Data analysis

Data analysis was performed with Statistica 10.0 for Windows. Distribution of the behavioral measures did not deviate from normality with the exception of the BRIEF-A Self-Monitor (Kholmogorov-Smirnov $d = .14$, $P < .05$) and SPQ-74 Disorganized factor ($d = .16$, $P < .05$) scores. To test genetic associations, a two-way factorial multivariate analysis of variance (MANOVA) was conducted, where genotype and gender were the between subjects factors and all twelve BRIEF-A measures served as dependent variables. Gender was controlled for due to the data suggesting its moderating role in gene effects (e.g., Cerasa et al., 2014). A separate MANOVA was run for each gene. Genotypes were grouped as follows: at least one minor allele of any biallelic polymorphism vs. homozygosity for its major allele; at least one *DRD4* long allele (≥ 6 repeats) vs. homozygosity for shorter alleles. Partial eta squared (η^2) or R^2 was calculated in order to investigate effect sizes. To investigate a potential mediating or modulating role of cognitive and personality variables in genetic associations, we first calculated Pearson correlations between these variables and those BRIEF-A measures for which a genotype effect was found during the first stage of the analysis. The significance level for raw *P*-values was set at .05, two-tailed. To address the multiple testing problem, we controlled false discovery rate (FDR) for MANOVA omnibus effects and Pearson correlations using Benjamini and Hochberg's procedure at the level of $q < .10$. Next, a backward stepwise linear regression method was used to select the most powerful predictors of the BRIEF-A measures among cognitive and personality parameters which were significantly correlated with the respective BRIEF-A measure. Finally, the MANOVA was repeated, with significant cognitive or personality predictors being added into the model. As the number (n) of individuals in each analysis slightly varied by availability of cognitive and personality data or genotypes, all (n) are presented with the results.

Results

BRIEF-A Data

Sixteen (16%) of the summary composite scores were within the clinically elevated range (defined as a *T* score of 65 or greater), and 56 of 100 individuals had at least one clinically elevated BRIEF-A scale. Analysis of Pearson correlations and *t*-tests demonstrated that BRIEF-A scores did not depend on age or gender.

Genetic associations

Table 1 presents genotype and minor allele frequencies for biallelic polymorphisms. The genotype frequencies were in Hardy-Weinberg equilibrium (all $P > .05$). Among *DRD4* alleles, the four-repeat allele was the most common (.71), followed by the seven-repeat allele (.19). Frequencies of the other alleles were .05 for 2R,

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Table 1. *Genotypes and alleles frequencies*

Polymorphism	Genotype number (frequency)			Minor allele frequency
COMT Val158Met (rs4680) *n* = 100	ValVal	ValMet	MetMet	
	28 (.28)	45 (.45)	27 (.27)	.50
DRD2 Taq1A (rs1800497) *n* = 94	CC	CT	TT	
	66 (.70)	24 (.26)	4 (.04)	.17
SLC64A 5-HTTLPR *n* = 98	LL	LS	SS	
	37 (.38)	47 (.48)	14 (.14)	.38
HTR2A G-1438A (rs6311) *n* = 95	GG	GA	AA	
	35 (.37)	44 (.46)	16 (.17)	.40

.04 for 3R, .01 for 5R, and .005 for 6R. These were similar to allele frequencies reported for other cohorts of European origin.

The MANOVA revealed a main effect of the 5-HTTLPR polymorphism (n = 98, Wilk λ = .76, $F_{12, 83}$ = 2.21, P = .018, η^2 = .24) on the BRIEF-A measures which survived the FDR-correction ($P_{corrected}$ = .09) (Table 2). Within the MANOVA, the genotype main effect was significant for the Plan/Organize ($F_{1, 94}$ = 7.34, P = .008, η^2 = .07), Task Monitor ($F_{1, 94}$ = 4.33, P = .04, η^2 = .04), and MI ($F_{1, 94}$ = 4.21, P = .043, η^2= .04). Carriers of the short allele reported significantly fewer problems than individuals homozygous for the long allele.

We subsequently ran the same analysis using co-dominant (LL vs. LS vs. SS) and recessive (LL+LS vs. SS) models of inheritance. In both cases MANOVA revealed neither genotype main effect nor effect of its interaction with gender on the BRIEF-A measures (all uncorrected P-values > .05).

Table 2. *Means and SD of BRIEF-A scores by gender and 5-HTTLPR genotype*

	Genotype LL			Genotype S+			LL vs. S+ significance level
BRIEF-A measures	women *n* = 21	men *n* = 16	all *n* = 37	women *n* = 40	men *n* = 21	all *n* = 61	
Inhibition	54.19	56.13	55.03	53.48	52.71	53.21	ns
	10.05	*10.46*	*10.13*	*8.14*	*10.98*	*9.13*	
Shift	60.57	62.25	61.30	60.05	54.14	58.02	ns
	7.59	*11.85*	*9.54*	*11.12*	*10.65*	*11.23*	
Emotional Control	57.81	61.63	59.46	61.58	53.67	58.85	ns
	9.02	*11.34*	*10.12*	*10.12*	*10.01*	*10.69*	
Self-Monitor	46.90	51.38	48.84	48.50	46.38	47.77	ns
	7.80	*9.73*	*8.85*	*8.18*	*7.42*	*7.93*	
Behavioral Regulation Index	56.57	60.38	58.22	58.10	52.48	56.16	ns
	7.84	*11.22*	*9.50*	*8.81*	*9.31*	*9.31*	
Initiate	50.90	56.56	53.35	53.08	48.67	51.56	ns
	8.79	*11.41*	*10.26*	*9.70*	*6.26*	*8.87*	
Working Memory	56.43	54.19	55.46	54.70	49.96	53.07	ns
	10.07	*7.93*	*9.15*	*10.09*	*7.87*	*9.59*	
Plan/Organize	54.38	56.31	55.22	52.35	48.24	50.93	P = .008
	8.54	*11.42*	*9.79*	*8.79*	*6.03*	*8.14*	
Task Monitor	60.33	58.75	59.65	55.95	54.95	50.61	P = .04
	9.38	*7.36*	*8.49*	*9.48*	*9.69*	*9.48*	
Organization of materials	54.33	52.25	53.43	50.98	49.86	50.59	ns
	10.22	*7.85*	*9.21*	*10.21*	*10.92*	*10.38*	
Metacognition Index	55.33	56.19	55.70	53.68	50.10	52.44	P = .043
	9.29	*9.09*	*9.08*	*9.36*	*6.93*	*8.71*	
GEC	56.62	58.69	57.51	57.13	51.05	55.03	ns
	8.07	*10.18*	*8.96*	*11.39*	*7.45*	*10.55*	

Notes: LL - homozygosity for the long allele of the 5-HTTLPR polymorphism; S+ - at least one short allele in genotype; ns – not significant.

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Potential mediating and moderating variables

None of the three measures (Plan/Organize, Task Monitor, MI) was correlated with the neuropsychological indicators. At the same time, all three were tightly related to personality variables reflecting negative affect, schizotypy and response style (Table 3).

The regression analysis showed that trait anxiety was a single significant predictor of the BRIEF-A measures. It correlated positively with the Plan/Organize ($n = 93$, $\beta = 0.46$, $t_{88} = 4.40$, $P = .001$, $R^2_{adj} = .17$), Task Monitor ($\beta = 0.57$, $t_{88} = 5.58$, $P = .001$, $R^2_{adj} = .25$), and Metacognition ($\beta = 0.57$, $t_{88} = 5.82$, $P = .001$, $R^2_{adj} = .27$).

We then repeated the MANOVA, which was based on the LL vs. S+ grouping of 5-HTTLPR genotype, adding the trait anxiety as a categorical variable into the model. To do this, participants were divided into low-anxious and high-anxious individuals using a median split on the Trait Anxiety scale (high trait anxiety > 44 scores). The Trait Anxiety value was significantly associated with the BRIEF-A scores overall ($n = 91$, Wilk $\lambda = .71$, $F_{12, 72} = 2.48$, $P = .009$, $\eta^2 = .29$) and with each of the twelve BRIEF-A measures (all $P < .05$). The genotype effect remained significant overall (Wilk $\lambda = .73$, $F_{12, 72} = 2.19$, $P = .021$, $\eta^2 = .27$) and for the Plan/Organize ($F_{1, 83} = 5.15$, $P = .026$, $\eta^2 = .06$) and Task Monitor ($F_{1, 83} = 4.51$, $P = .037$, $\eta^2 = .05$), but not MI ($F_{1, 83} = 3.51$, $P = .06$, $\eta^2 = .04$). There were no "genotype X trait anxiety" interaction effects. Of importance, the categorical trait anxiety measure was not related to 5-HTTLPR genotype ($n = 91$, Pearson $\chi^2 = 1.76$, $df = 1$, $P = .18$).

A pilot comparison of the LL and S+ genotype carriers on all the personality and neuropsychological measures with the *t*-test showed that the LL homozygotes had higher scores on most personality scales, with differences on the MMPI Depression and Social Introversion scales reaching the significance level ($n = 91$, Depression, $t = 2.97$, $P_{corrected} = .028$; Social Introversion, $t = 2.48$, $P_{corrected} = .083$). In addition, they performed worse on the Semantic Verbal Fluency test and TMT-B (verbal fluency, $n = 88$, $t = 3.11$, $P_{corrected} = .028$; TMT-B, $n = 69$, $t = 3.14$, $P_{corrected} = .028$) (Suppl. table 1).

Discussion

Our results indicate that the 5-HTTLPR polymorphism in the serotonin transporter gene may influence self-rating of everyday executive functioning in healthy individuals. Participants with at least one S allele showed lower scores on the Plan/Organize and Task Monitor scales and Metacognition index of the BRIEF-A than individuals homozygous for the long allele. The Metacognition index represents the ability to cognitively manage problem solving. Its Plan/Organize scale contains items related to setting a goal and selecting methods and steps to attain it, along with bringing order to

Table 3. *Means and SD of personality and cognitive measures and their correlations with the BRIEF-A scales*

Variables	Mean *SD*	BRIEF-A Plan/Organize	BRIEF-A Task Monitor	BRIEF-A Metacognition
STAI Trait Anxiety ($n = 93$)	44.43 *8.27*	.42****	.51****	.53****
MMPI L ($n = 92$)	44.91 *8.43*	–.13	–.16	–.20
MMPI F	58.36 *14.14*	.28**	.23*	.33***
MMPI K	50.18 *10.84*	–.24**	–.27**	–.31***
MMPI Hypochondriasis	52.15 *10.18*	.12	.22*	–.27**
MMPI Depression	51.25 *11.88*	.30**	.35***	.40****
MMPI Hysteria	53.13 *10.54*	.15	.22*	.28**
MMPI Psychopathic Deviate	52.84 *11.05*	.05	.20	.18
MMPI Masculinity/Femininity	51.97 *10.69*	.12	.06	.12
MMPI Paranoia	50.64 *11.41*	.08	.05	.10
MMPI Psychasthenia	55.62 *12.41*	.39****	.39****	.44****
MMPI Schizophrenia	53.97 *13.68*	.30**	.33***	.37****
MMPI Hypomania	57.00 *12.47*	.07	.09	.10
MMPI Social Introversion	51.76 *11.66*	.35***	.31**	.36****
SPQ-74 Total Score ($n = 91$)	17.79 *10.69*	.29**	.25**	.27**
SPQ-74 Cognitive-Perceptual Factor	7.27 *5.80*	.14	.14	.15
SPQ-74 Interpersonal Factor	8.56 *5.91*	.27**	.21*	.23*
SPQ-74 Disorganized Factor	3.82 *2.95*	.31**	.28**	.30**
Verbal Fluency ($n = 88$)	42.69 *9.05*	–.14	–.02	–.005
TMT-B ($n = 70$)	104 *44*	.21	.19	.20
Serial Subtractions ($n = 80$)	18.69 *6.80*	–.18	–.06	–.12
Stroop test, interference score ($n = 71$)	1.92 *7.44*	–.01	.03	.07

Notes: *$P_{corrected} < .10$; ** < .05; *** < .01, **** = .001.

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goal-relevant information, actions or materials. The Task Monitor scale measures the ability to keep track of one's own success and failure during the task-oriented activity.

The serotonin transporter is an important regulator of 5-HT transmission as it mediates the intracellular reuptake of released serotonin and modulates the concentration of serotonin in extracellular fluids. The 5-HTTLPR polymorphism is supposed to influence the serotonin transporter functions, though the evidence is not completely uniform (Lesch et al., 1996; Mann et al., 2000). Specifically, the presence of one or two S alleles is associated with reduced transcriptional efficiency of the gene that results in a significant decrease in serotonin reuptake (Lesch et al., 1996). The S allele has been previously linked to enhanced emotional reactivity and vulnerability to depression (Karg, Burmeister, Shedden, & Sen, 2011; Pergamin-Hight, Bakermans-Kranenburg, van Ijzendoorn, & Bar-Haim, 2012). Growing evidence also suggests that the 5-HTTLPR modulation extends to cognitive processes including EF (Homberg & Lesch, 2011). While a number of studies have shown that the S allele is associated with a relative impairment of cognitive processes (Holmes et al., 2010; Weiss et al., 2014), other authors have reported improved EF in the S allele carriers compared to individuals homozygous for the long allele (Borg et al., 2009; Enge, Fleischhauer, Lesch, Reif, & Strobel, 2011; Landrø et al., 2015). Our findings are consistent with these latter results, in that we observed that individuals carrying the short allele rated their problems in task planning and monitoring lower than individuals with the LL genotype.

A tendency to report fewer executive problems, however, could have various sources, including true high executive functioning, as well as hypoawareness of owns problems, or a response bias. In the present study, in accordance with the initial hypothesis, subjective rating of executive functioning was not related to performance on neuropsychological EF tasks, though the LL genotype carriers showed inferior results in tasks involving set-shifting (Verbal Fluency and TMT-B) as compared to individuals possessing the S-allele. At the same time, the subjective EF rating did correlate with individual's self -reported negative affect as well as with a spectrum of other self-reported psychological problems and response style indicators. In particular, the BRIEF-A measures correlated positively with anxiety-related traits and negatively with the MMPI K scale reflecting a tendency to present oneself in the best possible way. In addition, the S-allele carriers rated themselves lower on most personality scales. Overall, these results are in accord with the ideas that a response style, which itself might be related to anxiety level (Linden, Paulhus, & Dobson, 1986), can influence BRIEF-A scores and that lower BRIEF-A scores in carriers of the S allele could be explained, in part, by their increased social conformity (Homberg & Lesch, 2011). However, when we controlled for an anxiety level, the association of the 5-HTTLPR polymorphism with metacognition characteristics remained significant. This suggests that negative affect and/or response bias do not fully mediate or moderate the above association in healthy individuals. Moreover, the evidence of the 5-HTTLPR polymorphism's association with self-reported task planning and monitoring is in line with previous event-related potential and functional magnetic resonance imaging studies that have shown a 5-HTTLPR role in performance monitoring using behavioral paradigms (Althaus et al., 2009; Fallgatter et al., 2004; Fischer, Endrass, Reuter, Kubisch, & Ullsperger, 2015; Holmes et al., 2010), however, see (Olvet, Hatchwell, & Hajcak, 2010). Specifically, the short allele was related to either an enhanced error-related negativity (Althaus et al., 2009; Fallgatter et al., 2004), an electrophysiological correlate of error processing, or to post-error slowing (Fischer et al., 2015). These findings suggested that carriers of the short allele processed errors more intensively. However, no associations between the 5-HTTLPR polymorphism and post-error accuracy were found (Fallgatter et al., 2004; Fischer et al., 2015). Furthermore, as a whole, data on the relationships between these correlates of error-processing and post-error improvements in accuracy are contradictory (Danielmeier & Ullsperger, 2011). Thus, it is not quite clear whether the enhanced error processing in carriers of the S allele should correspond to higher or lower self-rating of the ability to keep track of one's own success and failure.

It is worth noting that our results point to the dominance for the lower functioning S-allele, which is in accord with some other studies (e.g., Stoltenberg & Vandever, 2010). At the same time the directionality of the 5-HTTLPR associations with the BRIEF-A and personality measures may seem unexpected as the short allele is supposed to be associated with vulnerability to depression and biased processing of negative stimuli (Karg et al., 2011; Pergamin-Hight et al., 2012). Our result can be interpreted based on the hypothesis, according to which rather than predisposing to development of anxiety-related traits the short allele is associated with greater responsiveness to environment and, in the presence of positive life events, may be related to an increased life-satisfaction and decreased depression (Belsky et al., 2009; Kuepper et al., 2012). Thus, the lower scores of the S-allele carriers on scales measuring psychological problems including depressive mood could be explained by the fact that our sample was comprised of healthy, well-educated and apparently problem-free subjects.

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The present study is a pilot one and has some limitations. First of all, the sample size was relatively small, having about 62% power to reveal effects of .05 (as computed for GEC with Quanto). So the study may have insufficient power to reveal associations of the BRIEF-A with the dopaminergic and *5-HTR2A* genes, which could be found in a larger sample. Further, our data indicate that there are a number of factors, including a response style, depressive mood and trait anxiety that may influence the BRIEF-A scores and presumably their associations with different genes. Though we controlled for some of potential confounders, there could exist others which were not taken into account in the present study. Clearly, further work is required to confirm and fully characterize the effect of 5-HTTLPR genotype on self-reported executive functioning. In particular, future research needs to take into account other polymorphisms in the serotonin transporter gene, especially the single nucleotide polymorphism (SNP) rs25531 located in the close proximity to the 5-HTTLPR. This SNP has been reported to modulate transcriptional activity of the L allele so that the L_G variant is functionally equivalent to the S-allele (Hu et al., 2006). Since the L_G variant is relatively rare in Caucasians (9–15%), it is unlikely that it has affected the result of the present study. However, it would be interesting to assess its influence on self-reported executive functioning in larger samples. In addition, given that the relationships between self-reported and objective measures of task planning and monitoring are not clear, future studies may benefit from investigating behavioral and subjective indicators of these abilities in the same individuals.

In summary, we investigated for the first time the associations between several candidate genes for cognitive control and self-reported executive functioning in daily life. The study provides evidence that the 5-HTTLPR polymorphism may influence self-report measures of executive functions and further supports the notion that performance monitoring may be influenced by the serotonin transporter gene. In addition, the results underscore the necessity to control for negative mood and a response bias while examining associations between genes and executive functioning measured with the self-report version of the BRIEF-A.

Supplementary Material

To view supplementary material for this article, please visit https://doi.org/10.1017/sjp.2017.6.

References

Alfimova M., Korovaitseva G., Lezheiko T., & Golimbet V. (2014). Interaction effects of the COMT and DRD4 genes with anxiety-related traits on selective attention. *The Spanish Journal of Psychology*, *17*, E-44. https://doi.org/10.1017/sjp.2014.46

Althaus M., Groen Y., Wijers A. A., Mulder L. J. M., Minderaa R. B., Kema I. P., … Hoekstra P. J. (2009). Differential effects of 5-HTTLPR and DRD2/ANKK1 polymorphisms on electrocortical measures of error and feedback processing in children. *Clinical Neurophysiology*, *120*, 93–107. https://doi.org/10.1016/j.clinph.2008.10.012

Barnes J. J. M., Dean A. J., Nandam L. S., O'Connell R. G., & Bellgrove M. A. (2011). The molecular genetics of executive function: Role of monoamine system genes. *Biological Psychiatry*, *69*, e127–e143. https://doi.org/10.1016/j.biopsych.2010.12.040

Belsky J., Jonassaint C., Pluess M., Stanton M., Brummett B., & Williams R. (2009). Vulnerability genes or plasticity genes? *Molecular Psychiatry*, *14*, 746–754. https://doi.org/10.1038/mp.2009.44

Berezin F., Miroshnikov M., & Rozhanets R. (1976). *Method of multiphasic investigation of personality in clinical medicine and psychological hygiene*. Moscow, Russia: Meditsina.

Borg J., Henningsson S., Saijo T., Inoue M., Bah J., Westberg L., … Farde L. (2009). Serotonin transporter genotype is associated with cognitive performance but not regional 5-HT1A receptor binding in humans. *The International Journal of Neuropsychopharmacology*, *12*, 783. https://doi.org/10.1017/s1461145708009759

Cerasa A., Quattrone A., Piras F., Mangone G., Magariello A., Fagioli S., … Spalletta G. (2013). 5-HTTLPR, anxiety and gender interaction moderates right amygdala volume in healthy subjects. *Social Cognitive and Affective Neuroscience*, *9*, 1537–1545. https://doi.org/10.1093/scan/nst144

Ciszewski S., Francis K., Mendella P., Bissada H., & Tasca G. A. (2014). Validity and reliability of the Behavior rating inventory of executive function — adult version in a clinical sample with eating disorders. *Eating Behaviors*, *15*, 175–181. https://doi.org/10.1016/j.eatbeh.2014.01.004

Cuthbert B., & Insel T. (2013). Toward precision medicine in psychiatry: The NIMH Research Domain Criteria project. In D. Charney, J. Buxbaum, P. Sklar, & E. Nestler (Eds.), *Neurobiology of mental illness* (4th Ed., pp. 1076–1088). New York, NY: Oxford University Press.

Danielmeier C., & Ullsperger M. (2011). Post-error adjustments. *Frontiers in Psychology*, *2*, 233. https://doi.org/10.3389/fpsyg.2011.00233

Diamond A. (2013). Executive functions. *Annual Review of Psychology*, *64*, 135–168. https://doi.org/10.1146/annurev-psych-113011-143750

Eisenberg D. P., & Berman K. F. (2010). Executive function, neural circuitry, and genetic mechanisms in schizophrenia. *Neuropsychopharmacology*, *35*, 258–277. https://doi.org/10.1038/npp.2009.111

Enge S., Fleischhauer M., Lesch K. P., Reif A., & Strobel A. (2011). Serotonergic modulation in executive functioning: Linking genetic variations to working memory performance. *Neuropsychologia*, *49*, 3776–3785. https://doi.org/10.1016/j.neuropsychologia.2011.09.038

Etkin A., Gyurak A., & O'Hara R. (2013). A neurobiological approach to the cognitive deficits of psychiatric disorders. *Dialogues in Clinical Neuroscience*, *15*, 419–429.

Fallgatter A. J., Herrmann M. J., Roemmler J., Ehlis A. C., Wagener A., Heidrich A., … Lesch K. P. (2004).

Allelic variation of serotonin transporter function modulates the brain electrical response for error processing. *Neuropsychopharmacology*, *29*, 1506–1511. https://doi.org/10.1038/sj.npp.1300409

Fischer A. G., Endrass T., Reuter M., Kubisch C., & Ullsperger M. (2015). Serotonin reuptake inhibitors and serotonin transporter genotype modulate performance monitoring functions but not their electrophysiological correlates. *Journal of Neuroscience*, *35*, 8181–8190. https://doi.org/10.1523/jneurosci.5124-14.2015

Garlinghouse M. A., Roth R. M., Isquith P. K., Flashman L. A., & Saykin A. J. (2010). Subjective rating of working memory is associated with frontal lobe volume in schizophrenia. *Schizophrenia Research*, *120*, 71–75. https://doi.org/10.1016/j.schres.2010.02.1067

Golimbet V. E., Alfimova M. V., & Mityushina N. G. (2004). Polymorphism of the serotonin 2A receptor gene (5HTR2A) and personality traits. *Molecular Biology*, *38*, 337–344. https://doi.org/10.1023/b:mbil.0000032202.83988.09

Golimbet V. E., Korovaitseva G. I., Brusov O. S., Faktor M. I., Ganisheva T. K., & Dmitriev D. A. (2010). The functional state of the serotonergic system and the 5-HTTLPR polymorphism of the serotonin transporter gene in patients with schizophrenia. *Molecular Biology*, *44*, 223–227. https://doi.org/10.1134/s0026893310020068

Holmes A. J., Bogdan R., & Pizzagalli D. A. (2010). Serotonin transporter genotype and action monitoring dysfunction: A possible substrate underlying increased vulnerability to depression. *Neuropsychopharmacology*, *35*, 1186–1197. https://doi.org/10.1038/npp.2009.223

Homberg J. R., & Lesch K. P. (2011). Looking on the bright side of serotonin transporter gene variation. *Biological Psychiatry*, *69*, 513–519. https://doi.org/10.1016/j.biopsych.2010.09.024

Hosenbocus S., & Chahal R. (2012). A review of executive function deficits and pharmacological management in children and adolescents. *Journal of the Canadian Academy of Child and Adolescent Psychiatry*, *21*, 223–229.

Hu X. Z., Lipsky R. H., Zhu G., Akhtar L. A., Taubman J., Greenberg B., … Goldman D. (2006). Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. *American Journal of Human Genetics*, *78*, 815–826. https://doi.org/10.1086/503850

Karg K., Burmeister M., Shedden K., & Sen S. (2011). The serotonin transporter promoter variant (5-HTTLPR), stress, and depression: Meta-analysis revisited. *Archive of General Psychiatry*, *68*, 444–454. https://doi.org/10.1001/archgenpsychiatry.2010.189

Kuepper Y., Wielpuetz C., Alexander N., Mueller E., Grant P., & Hennig J. (2012). 5-HTTLPR S-allele: A genetic plasticity factor regarding the effects of life events on personality? *Genes, Brain, and Behavior*, *11*, 643–650. https://doi.org/10.1111/j.1601-183X.2012.00783.x

Landrø N. I., Jonassen R., Clark L., Haug K. B. F., Aker M., Bø R., … Stiles T. C. (2015). Serotonin transporter polymorphisms predict response inhibition in healthy volunteers. *Neuroscience Letters*, *584*, 109–112. https://doi.org/10.1016/j.neulet.2014.10.006

Lane H., Liu Y., Huang C., Hsieh C., Chang Y., Chang L., … Chang W. (2008). Prefrontal executive function and D1, D3, 5-HT2A and 5-HT6 receptor gene variations in healthy adults. *Journal of Psychiatry & Neuroscience*, *33*, 47–53.

Lesch K. P., Bengel D., Heils A., Sabol S. Z., Greenberg B. D., Petri S., … Murphy D. L. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*, *274*, 1527–1531. https://doi.org/10.1126/science.274.5292.1527

Linden W., Paulhus D. L., & Dobson K. S. (1986). Effects of response styles on the report of psychological and somatic distress. *Journal of Consulting and Clinical Psychology*, *54*, 309–313. https://doi.org/10.1037/0022-006x.54.3.309

Logue S. F., & Gould T. J. (2014). The neural and genetic basis of executive function: Attention, cognitive flexibility, and response inhibition. *Pharmacology, Biochemistry and Behavior*, *123*, 45–54. https://doi.org/10.1016/j.pbb.2013.08.007

Mann J. J., Huang Y. Y., Underwood M. D., Kassir S. A., Oppenheim S., Kelly T. M., … Arango V. (2000). A serotonin transporter gene promoter polymorphism (5-HTTLPR) and prefrontal cortical binding in major depression and suicide. *Archive of General Psychiatry*, *57*, 729–738. https://doi.org/10.1001/archpsyc.57.8.729

Monakhov M., Golimbet V., Abramova L., Kaleda V., & Karpov V. (2008). Association study of three polymorphisms in the dopamine D2 receptor gene and schizophrenia in the Russian population. *Schizophrenia Research*, *100*, 302–307. https://doi.org/10.1016/j.schres.2008.01.007

NIMH (2011). *Cognitive systems: Workshop proceedings*. Rockville, MD: Author. Retrieved from http://www.nimh.nih.gov/research-priorities/rdoc/cognitive-systems-workshop-proceedings.shtml

Olvet D. M., Hatchwell E., & Hajcak G. (2010). Lack of association between the 5-HTTLPR and the error-related negativity (ERN). *Biological Psychology*, *85*, 504–508. https://doi.org/10.1016/j.biopsycho.2010.09.012

Pergamin-Hight L., Bakermans-Kranenburg M., van IJzendoorn M., & Bar-Haim Y. (2012). Variations in the promoter region of the serotonin transporter gene and biased attention for emotional information: A meta-analysis. *Biological Psychiatry*, *71*, 373–379. https://doi.org/10.1016/j.biopsych.2011.10.030

Rabin L. A., Roth R. M., Isquith P. K., Wishart H. A., Nutter-Upham K. E., Pare N., … Saykin A. J. (2006). Self- and informant reports of executive function on the BRIEF-A in MCI and older adults with cognitive complaints. *Archives of Clinical Neuropsychology*, *21*, 721–732. https://doi.org/10.1016/j.acn.2006.08.004

Raine A. (1991). The SPQ: A scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophrenia Bulletin*, *17*, 555–564. https://doi.org/10.1093/schbul/17.4.555

Roca M., Vives M., López-Navarro E., García-Campayo J., & Gili M. (2015). Cognitive impairments and depression: A critical review. *Actas Españolas de Psiquiatría*, *43*, 187–193.

Roth R., Isquith P., & Gioia G. (2005). *Behavioral rating inventory of executive function—adult version*. Lutz, FL: Psychological Assessment Resources.

Spielberger C., & Gorsuch R. (1983). *Manual for the State-trait anxiety inventory (form Y) ("self-evaluation questionnaire")*. Palo Alto, CA: Consulting Psychologists Press.

Spreen O., Strauss E., & Sherman E. (2006). *A compendium of neuropsychological tests*. New York, NY: Oxford University Press.

Stoltenberg S. F., & Vandever J. M. (2010). Gender moderates the association between 5-HTTLPR and decision-making under ambiguity but not under risk. *Neuropharmacology*, *58*, 423–428. https://doi.org/10.1016/j.neuropharm.2009.09.010

Unoka Z., & Richman M. J. (2016). Neuropsychological deficits in BPD patients and the moderator effects of co-occurring mental disorders: A meta-analysis. *Clinical Psychology Review*, *44*, 1–12. https://doi.org/10.1016/j.cpr.2015.11.009

Vriezen E., & Pigott S. (2002). The relationship between parental report on the BRIEF and performance-based measures of executive function in children with moderate to severe traumatic brain injury. *Child Neuropsychology*, *8*, 296–303. https://doi.org/10.1076/chin.8.4.296.13505

Weiss E. M., Schulter G., Fink A., Reiser E. M., Mittenecker E., & Niederstätter H., … Papousek I. (2014). Influences of COMT and 5-HTTLPR polymorphisms on cognitive flexibility in healthy women: Inhibition of prepotent responses and memory updating. *Plos ONE*, *9*, e85506. https://doi.org/10.1371/journal.pone.0085506

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