A Hierarchical Factor Model of Executive Functions in Adolescents: Evidence of Gene-Environment Interplay

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Abstract

Executive functions (EF) are a complex set of neurodevelopmental, higher-ordered processes that are especially salient during adolescence. Disruptions to these processes are predictive of psychiatric problems in later adolescence and adulthood. The objectives of the current study were to characterize the latent structure of EF using bifactor analysis and to investigate the independent and interactive effects of genes and environments on EF during adolescence. Using a representative young adolescent sample, we tested the interaction of a polymorphism in the serotonin transporter gene (*5-HTTLPR*) and parental supervision for EF through hierarchical linear regression. To account for the possibility of a hierarchical factor structure for EF, a bifactor analysis was conducted on the eight subtests of the Delis-Kaplan Executive Functions System (D-KEFS). The bifactor analysis revealed the presence of a general EF construct and three EF sub-domains (i.e., conceptual flexibility, inhibition, and fluency). A significant *5-HTTLPR* by parental supervision interaction was found for conceptual flexibility, but not for general EF, fluency or inhibition. Specifically, youth with the L/L geno-type had significantly lower conceptual flexibility scores compared to youth with S/S or S/L genotypes given low levels of parental supervision. Our findings indicate that adolescents with the L/L genotype were especially vulnerable to poor parental supervision on EF. This vulnerability may be amenable to preventive interventions. (JINS, 2015, *21*, 62–73)

Keywords: Executive functions, Bifactor model, Adolescence, Gene-environment interaction, 5-HTTLPR, Parental supervision

INTRODUCTION

Adolescence is a critical period for cognitive and emotional development, particularly for executive functioning (EF; Crone, 2009), which are neurocognitive processes that regulate and maintain higher-order actions and goal oriented behaviors (Barkley, 1997). During adolescence, typically developing youth improve in their abilities to regulate and plan their actions and thoughts (Huizinga, Dolan, & Van der Molen, 2006). The degree of maturation in adolescent regulatory abilities is thought to reflect neurobiological development and influences risk behaviors, including disruptive behavior (Hobson, Scott & Rubia, 2011; Matthys, Vanderschuren, & Schutter, 2013) and substance use

disorders (Clark et al., 2013; Giancola & Tarter, 1999). Adolescent development is also strongly influenced by environmental factors, such as parenting behaviors (Clark, Thatchere, & Maisto, 2004; Clark, Kirisci, Mezzich, & Chung, 2008) and deviant peers (Huizinga et al., 2006). However, relatively little is known about how environmental and heritable factors interact to influence EF during this developmental epoch.

Regarding the taxonomy of EF, a tripartite framework has been proposed (Miyake, Friedman, Rettinger, Shah, & Hegarty, 2001), consisting of three distinct but moderately correlated factors. These dimensions include *set-shifting* [i.e., the ability to shift back and forth between multiple tasks, operations or mental sets (Monsell, 1996)], *updating and monitoring* [i.e., the ability to monitor and code information relevant to the task and manipulate the information appropriately when new information is provided; also similar to working memory (Goldman-Rakic, 1996)], and *inhibition* [i.e., the ability to deliberately suppress a dominant response

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in the presence of a nonessential stimuli (Logan, Schachar, & Tannock, 1997)]. However, emerging research suggests that the factor structure of EF may vary by age, particularly across childhood and adolescence (Huizinga et al., 2006; Lee, Bull, & Ho, 2013; Prencipe et al., 2011; Zelazo, Craik, & Booth, 2004). A two factor structure, representing inhibition and switching, was the best fit to the data during early to late childhood, but a three factor model, representing inhibition, updating, and switching, became the best fit to the data during adolescence (Lee et al., 2013). Prencipe and colleagues (2011) distinguished between "hot" (i.e., motivationally salient) and "cool" (i.e., abstract) EF tasks in a typically developing sample between 8 and 15 years of age and found that improvements in cool EF tasks (i.e., Color-Word Stroop, Backward Digit Span) began during the earlier aged cohorts, whereas improvements in "hot" tasks (i.e., gambling task, delay-discounting) developed more gradually and were most robust in the adolescent cohort. However, in their exploratory factor analysis for all tasks, a single factor model emerged as the best fit to the data. This suggests that the factor structure of EF may be organized hierarchically, such that the covariation among EF components may be modeled as a single latent factor (Alarcón, Plomin, Fulker, Corley, & DeFries, 1998; Friedman et al., 2008), whereas each sub-dimension of EF may be defined by unique genetic and environmental pathways.

Twin studies have established the important role of genetic influences for variation in EF, with heritability estimates for inhibition, set-shifting, and monitoring/working memory ranging from 43% to 77% (Ando, Ono, & Wright, 2001; Coolidge, Thede, & Young, 2000; Kuntsi et al., 2006). While the search for specific genes associated with EF have been elusive, one particular candidate system with implications for EF is serotonin (5-HT; see Logue & Gould, 2014). The role of 5-HT in the development of EF is partly related to the expression of 5-HT in the prefrontal cortex (PFC; Puig & Gulledge, 2011), a region of the brain that is known to regulate higher order functions such as learning, working memory, and behavioral flexibility (Fuster, 2001; also see Blakemore & Choudhury, 2006). Serotonergic receptors are largely expressed in the PFC, which regulate 5-HT activity (Enge, Fleischhaauer, Lesch, Reif, & Strobel, 2011). Variations in extracellular 5-HT in the PFC have been associated with performance in response inhibition, reversal learning tasks and other EF tasks across human (Cools, Roberts, & Robbins, 2008; Crean, Richards, & de Wit, 2002) and nonhuman primate models (Homberg et al., 2007; Walker, Mikheenko, Argyle, Robbins, & Roberts, 2006), although associations with set-shifting abilities have been equivocal (Logue & Gould, 2014). Given the primacy of 5-HT regulation and EF performance in general, the functional polymorphism in the promoter region of the 5-HT transporter gene (*5-HTTLPR*) is a plausible candidate for EF, as the short (S) allele is known to convey reduced 5-HT transporter transcription (i.e., lower transporter levels) and subsequently reduced 5-HT reuptake than the long (L_a) allele (Hu et al., 2006). The A > G single nucleotide polymorphism

(SNP) has also been identified within the L allele and is functionally similar to the S allele (Hu et al., 2006).

Genetic association studies have shown a link between the S allele and increased sensitivity to stress and higher risk for depression (see meta-analysis by Karg, Burmeister, Shedden, & Sen, 2011), but *better* performance on EF (Weikum et al., 2013). However, it is unclear whether *5-HTTLPR* functionality is specific to any single domain of EF, or whether it is generally associated with EF performance. For example, a meta-analysis of youth with attention-deficit/hyperactivity disorder found an association between the L/L genotype and worse performance on measures of impulsivity, inattention, and working memory (Gizer, Ficks, & Waldman, 2009). Youth with the L/L genotype performed worse than non-L/L youth on EF tasks when their mothers endorsed high levels of depression symptoms, although they were also *better* than non-L/L youth on these tasks when their mothers endorsed few depression symptoms (Weikum et al., 2013). Adults carrying the L/L genotype performed worse on a tasks of risky decision making and visual planning (Roiser, Rogers, Cook, & Sahakian, 2006), set-shifting (Borg et al., 2009) and inhibition (Roiser et al., 2006) compared to individuals without this genotype. Taken together, these findings suggest that allelic variation in *5-HTTLPR* may also be associated with EF performance (Weikum et al., 2013). However, more research is needed to disentangle the possibility of specific *5-HTTLPR* effects as they relate to the various dimensions of EF.

Genetic influences for complex phenotypes are also widely believed to act in conjunction with environmental factors (i.e., gene-environment interaction; GxE), whereby genetic influences on a phenotype may be enhanced or attenuated as a function of the environment (or *vice versa*). An abundance of studies have examined GxE effects involving *5-HTTLPR* and harsh or severe parenting, including for depression (Gibb, Uhrlass, Grassia, Benas, & McGeary, 2009; Kaufman et al., 2004), aggression (Li & Lee, 2010; Reif et al., 2007), and attention-deficit/hyperactivity disorder (Retz et al., 2008). However, GxE studies for EF have yet to emerge. One particular environmental factor that may moderate the association between *5-HTTLPR* and EF is parental supervision (i.e., knowledge of child's whereabouts, availability). Parental supervision is a critical component of adolescent development, given its association with socioemotional (Li, Berk, & Lee, 2013; Wang, Pomerantz, & Chen, 2007), behavioral (Clark, Thatcher, & Maisto, 2005; Dishion & McMahon, 1998), and academic achievement (e.g., Li, Walker, & Armstrong, 2014; Soenens, Vansteenkiste, Luyckx, & Goossens, 2006) outcomes. The extant literature on parental supervision and adolescent cognitive and academic achievement has been mixed, as although some studies have found an association between higher parental supervision and better performance (e.g., Rankin & Quane, 2002), others have found null or inverse associations with performance (e.g., Li et al., 2014; Weiss & Schwarz, 1996). Despite evidence suggesting a role of parenting on the development of EF and related phenotypes, studies regarding the potential interplay of *5-HTTLPR* genotype and EF are lacking.

The aims of this study were to elucidate the latent architecture of EF and to investigate the interplay of *5-HTTLPR* and parental supervision on EF in adolescents. A hierarchical three-factor structure for EF was predicted, characterized by dimensions corresponding to those reported by previous studies (i.e., inhibition, working memory, and set-shifting; Friedman et al., 2008; Miyake et al., 2001), as a well as a higher-order general factor that would account for the covariation among the dimensions. Youth exposed to low parental supervision were predicted to have worse EF performance compared to youth reporting comparably higher parental supervision. In line with recent GxE findings (e.g., Weikum et al., 2013), it was also predicted that individuals carrying the L/L genotype would be more sensitive to environmental influences, such that youth carrying the L/L genotype would perform worse on EF in the presence of poor parental supervision compared to youth with the S/S or S/L genotypes.

METHOD

Participants

Adolescent participants ($N = 142$; ages 12–15 years) were recruited from the Pittsburgh area. All participants were a representative sample stratified by year of birth, sex, and race-ethnicity. Among these participants, genotype data were available for 116. All descriptive data can also be found in Table 1. Adolescents were identified through a neighborhood-based targeted random dialing telephone procedure. Successfully contacted families were screened for eligibility by staff at the University Center for Social and Urban Research (UCSUR) at the University of Pittsburgh. Eligible participants and their parents completed informed consent, a psychological assessment, and DNA collection. Written informed consent was obtained in person from a parent and assent from the adolescent before conducting any of the study procedures. The study protocol was approved by the university's Institutional Review Board.

Genotyping

We extracted DNA from saliva using a mouthwash protocol (King et al., 2002). Samples were subjected to whole genome amplification using the genomiphi protocol (Dean et al., 2002), quantified by the PicoGreen protocol, and diluted to 40 ng/μL for storage. A polymerase chain reaction protocol followed by double restriction endonuclease digestion was used to identify the *5-HTTLPR* and rs25531 variants: S, L_a, and L_g (Wendland, Martin, Kruse, Lesch, & Murphy, 2006). The primer sequences were: (forward) 5'-TCCTCCGC TTTGGCGCCTCTTCC-3', and (reverse) 5'-TGGGGGTT GCAGGGGAGATCCTG-3'. The L allele was subtyped for rs25531. The A > G SNP of rs25531 was concurrently detected by digesting the amplified fragments with *Msp*I (New England Biolabs, Beverly, MA), where the A > G substitution creates an additional *Msp*I site. Amplification products were simultaneously resolved by electrophoresis on

3.5% agarose gels. The L_a variant (528 bp) has approximately three times the basal activity of the S promoter (484 bp) with the deletion (Lesch et al., 1996).

The genotype distribution for the available sample was: S/S (16.4%; $n = 19$), S/L_g (10.3%; $n = 12$), L_g/L_g (1.7%; $n = 2$), (12.1%; $n = 14$) S/L_a (35.3%; $n = 41$), and L_a/L_a (24.1%; $n = 28$). Because the rare L_g and S allele are functionally equivalent, we combined the rs24431 SNP and *5-HTTLPR* polymorphism so that the variable had three levels: (1) "S/S," which includes S/S and S/L_g genotypes, (2) "S/L," which includes S/L_a and L_g/L_a genotypes, and (3) "L/L," which includes the L_a/L_a genotype. Following empirical precedent (Greenberg et al., 1999; Little et al., 1998), we dummy coded *5-HTTLPR* genotype where individuals carrying at least one copy of the low transcription alleles (i.e., S/S and S/L) were coded 0 and individuals carrying zero low transcription alleles (i.e., L/L) were coded 1. Genotype frequencies did not deviate significantly from Hardy-Weinberg equilibrium ($\chi^2 = .17$; $df = 1$).

Measures

Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001). The D-KEFS is a standardized neuropsychological assessment protocol with excellent psychometric properties. We used eight subtests of the D-KEFS: (1) Trail Making (attention, conceptual flexibility), (2) Verbal Fluency (processing speed, lexical organization), (3) Design Fluency (nonverbal processing speed), (4) Color-Word Interference (response inhibition, conceptual flexibility), (5), Sorting (conceptual flexibility), (6) Twenty Questions (deductive reasoning, working memory), (7) Word Context (deductive reasoning, conceptual flexibility, working memory), and (8) Tower (planning). Each test is described in greater detail in the D-KEFS manual (Delis et al., 2001). In line with previous studies and empirical precedent (i.e., Delis et al., 2001; Latzman & Markon, 2010), we used the D-KEFS Total Achievement Scaled scores (i.e., mean = 10; $SD = 2$) for our analyses. Means, standard deviations and effect sizes are presented in Table 1.

Loeber Youth Questionnaire, Supervision Subscale (LYQ; Jacob, Moser, Windle, Loeber, & Stouthamer-Loeber, 2000). The 58-item LYQ was completed by the adolescent. We used the supervision subscale, which consists of four items including (1) whether parents know where and (2) with whom he/she is with when away from home, (3) when he/she will return, and (4) whether he/she would be able to contact the parents when the parents are away from home. Adolescents responded to these questions by selecting the frequency of these items: "almost never," "sometimes," "almost always," and "does not apply." Psychometric properties of the LYQ have been described elsewhere (Loeber, Farrington, Stouthamer-Loeber, & Van Kammen, 1998). The internal consistency (Cronbach's alpha) of the scale in the current sample was adequate (.71).

Statistical Analyses

Analyses were conducted in Mplus 6.11 (Muthén & Muthén, 2010) using the full sample ($N = 142$). In the first step, we

Table 1. Demographic information and D-KEFS mean scores by *5-HTTLPR* genotype

	L/L	S/S + S/L	Test statistic	*p*	Cohen's *d*
*N**	28	88	—	—	—
Male (*n*)	14	46	$\chi^2(1) = .27$	.61	—
Mean age (*SD*)	14.11 (1.21)	14.19 (1.28)	$t = .51$	.66	.09
Racial-ethnic groups (*n*)	—	—	$\chi^2(3) = 1.02$	.80	—
European-American	21	62	—	—	—
African-American	8	27	—	—	—
Other	2	4	—	—	—
Parental education (*n*)	—	—	$\chi^2(4) = 5.32$	.26	—
GED	4	10	—	—	—
Partial college	5	20	—	—	—
College graduate	5	19	—	—	—
Partial graduate school	13	21	—	—	—
Masters level degree	4	23	—	—	—
Doctoral level degree	0	0	—	—	—
Mean LQAS composite score (*SD*)	10.91 (1.25)	10.62 (1.84)	$t = .94$	.35	.18
Mean D-KEFS scaled scores (*SD*)	—	—	—	—	—
Trails	9.52 (2.75)	9.97 (3.15)	$t = .75$	.45	.14
VF letter	9.37 (1.86)	9.42 (2.47)	$t = .09$	.93	.02
VF category	9.87 (2.99)	10.23 (3.13)	$t = .57$	.57	.10
VF switch	9.71 (2.83)	9.74 (3.70)	$t = .05$	.96	.01
VF accuracy	10.26 (2.56)	10.48 (3.17)	$t = .40$	.69	.07
Design Fluency	10.67 (3.97)	11.13 (3.31)	$t = .73$	.47	.13
CW inhibition	9.86 (2.88)	10.65 (3.26)	$t = 1.27$	.21	.23
CW switch	9.04 (3.28)	10.65 (2.47)	$t = 2.49$	.01	.45
Sorting correct	9.31 (2.69)	10.00 (3.00)	$t = 1.20$	.23	.22
Sorting description	9.37 (2.74)	9.90 (3.00)	$t = .92$	.36	.17
Sorting recognition	8.92 (3.47)	10.06 (3.56)	$t = 1.58$	.12	.29
Twenty Questions	11.33 (2.09)	11.48 (2.91)	$t = .33$	.74	.06
Word Context	10.57 (3.08)	10.81 (3.17)	$t = .37$	.71	.07
Tower	10.55 (1.95)	10.58 (2.20)	$t = .08$	.94	.01
Mean D-KEFS factor scores (*SD*)	—	—	—	—	—
Fluency	−0.09 (2.52)	−0.02 (2.82)	$t = .13$	.90	.02
Inhibition	−0.05 (.70)	0.21 (.57)	$t = 1.90$	.06	.34
Conceptual flexibility	0.03 (2.28)	0.07 (1.95)	$t = .09$	.93	.02
General factor	−0.07 (1.41)	0.28 (1.73)	$t = 1.11$	.27	.20

Note. Categorical variables were compared using Pearson's chi-squared tests, continuous variables were compared using an independent samples t-test; VF = Verbal Fluency; CW = Color-Word.
*Genotypic information was not available on the full sample (*n* = 116 out of 142).

established the optimal factor structure for the D-KEFS by conducting an exploratory factor analysis (EFA) with correlated factors (i.e., oblimin rotation) on the full correlation matrix using maximum likelihood estimation (see Satorra, 2003). A scree plot was examined for visual inspection of the best fitting factor structure. The Bayesian Information Criterion (BIC) was used to assess goodness-of-fit from models comprising of one to eight factors. In step 2, we fit a bifactor model using the best fitting factor model from the EFA. The bifactor model allows each item to have a positive loading on the general trait (which is assumed to underlie all items) as well as loadings on one or more "group" factors, which is assumed to be more conceptually narrow (Reise, Morizot, & Hays, 2007). Factor scores were derived based on the results of the bifactor model. In the final step, we conducted a hierarchical linear regression using the available genotypic sample (*n* = 116) to model: (1) main effects of parental supervision and *5-HTTLPR* genotype and (2) main effects plus the interaction of *5-HTTLPR* genotype and parental supervision for bifactor-derived EF variables. In all models, child age, sex (1 = male, 2 = female), self-reported race-ethnicity (1 = European-American, 2 = African-American, 3 = other), and parental education (1 = GED, 2 = partial college, 3 = college graduate, 4 = partial graduate school, 5 = masters level degree, 6 = doctoral level degree) were controlled.

RESULTS

Factor Analysis and Factor Score Derivation

Factor loadings for the best fitting EFA model are shown in Table 2. Comparison of the BIC values for one through eight

Table 2. Factor analysis of D-KEFS

Variable	Three factor EFA model			Three factor bifactor model			
	Conceptual flexibility	Inhibition	Fluency	g	Conceptual flexibility	Inhibition	Fluency
Trails	.11	**.63**	− .01	**.52**	.09	**.45**	− .04
VF letter	.02	.36	− .04	.28	.01	.21	.11
VF category	− .21	**.42**	.26	.31	− .20	.27	.31
VF switch	− .01	− .02	**.99**	.45	.01	.01	**.89**
VF accuracy	.05	.05	**.78**	.41	.01	− .02	**.85**
Design Fluency	.10	**.56**	.09	**.52**	.10	.38	.11
CW inhibition	.02	**.74**	.03	**.55**	.01	**.51**	− .01
CW switch	− .05	**.79**	− .06	**.51**	− .03	**.52**	− .04
Sorting correct	**.96**	− .02	.01	**.54**	**.80**	− .01	.00
Sorting description	**.99**	− .03	.01	**.56**	**.83**	− .01	.01
Sorting recognition	**.70**	.18	.02	**.54**	**.58**	.12	.02
Twenty Questions	.29	.22	− .07	.29	.20	.17	− .05
Word Context	.25	.32	.04	**.40**	.20	.19	.14
Tower	.12	.17	.01	.19	.11	.12	− .03

Note. EFA = exploratory factor analysis; g = general factor; VF = Verbal Fluency; CW = Color-Word.

factor models indicated that the three-factor model was optimal (i.e., smallest BIC value). Results of the scree plot also suggested that the three factor solution provided the best fit to the data (i.e., based on number of factors with eigenvalues >1) (table and figure are available upon request). Our findings are almost entirely consistent with those reported by Latzman and Markon (2010) among their 8- to 19-year-old subgroup. The Sorting tests, including Free Sort Correct (.96), Free Sort Description (.99), and Sort Recognition (.70), uniformly loaded onto a single dimension, which was labeled as "conceptual flexibility," because these tests require flexibility in thinking and behavior, manipulation of both verbal and nonverbal processes, and the ability to initiate problem solving, among other abilities (Greve, Farrell, Besson, & Crouch, 1995; Latzman & Markon, 2010). The second factor consisted of high factor loadings contributed by Trail Making (.63), Verbal Fluency Category Fluency (.42), Design Fluency (.56), Color-Word Inhibition (.74), and Color-Word Inhibition/Switching (.79). This domain was labeled "inhibition," given that these tasks measure the ability to inhibit overlearned responses across a variety of visual-motor tasks (Latzman & Markon, 2010). Finally, the third factor was represented by two tasks: Verbal Fluency Category Switching (.99) and Verbal Fluency Accuracy (.78). In contrast to Latzman and Markon (2010), factor loadings for Verbal Fluency Letter (− .04) and Category Fluency (.26) did not significantly load onto this dimension. We labeled this factor "fluency."

Next, we fit a three-factor bifactor model, with the purpose of determining whether the D-KEFS tests could be represented by a single general factor, whereas each subdomain (i.e., conceptual flexibility, inhibition, and fluency) could be represented by unique group factors. Factor loadings from the bifactor analysis are shown in Table 2 and graphically represented in Figure 1. Factor loadings on the general factor were consistently high (i.e., >.40) for most subtests of the D-KEFS, with the exceptions of Verbal Fluency Letter (.28), Category (.31), Twenty Questions (.29), and Tower (.19). As expected, factor loadings on the three group factors were relatively consistent with the three-factor EFA solution, although two subtests no longer loaded highly onto the inhibition domain: Verbal Fluency Category (.27) and Design Fluency (.38). The general factor accounted for 38% of the explained variance, whereas the conceptual flexibility, inhibition, and fluency group factors accounted for 24, 15, and 23% of the remaining variance, respectively. These findings indicate that a general factor is a significant contributor to subtest scores on the D-KEFS. Factor scores for the EF general factor, conceptual flexibility, inhibition and fluency were derived based on these results.

Gene-Environment Interaction

The bifactor solution was used to regress the general factor and the group factors on *5-HTTLPR* genotype, parental supervision, and their interaction within hierarchical linear regression models. In all models, race-ethnicity, sex, parental education, and child age were statistically controlled. Parameter estimates from these models are presented in Table 3. In the main effects models, we found a significant main effect for *5-HTTLPR* L/L genotype (B = − .55; *SE* = .27; *p* = .05), but not for parental supervision (B = .15; *SE* = .14; *p* = .31) on the EF general factor. Specifically, individuals with the L/L genotype had lower scores on the EF general factor. No main effects for *5-HTTLPR* or parental supervision were detected for conceptual flexibility, inhibition, or fluency. In the final (interaction) models, we detected a significant interactive effect of *5-HTTLPR* and parental supervision for conceptual flexibility (B = −1.18; *SE* = .45; *p* < .01) (Figure 2). *Post hoc* analyses indicated that parental supervision was significantly associated with
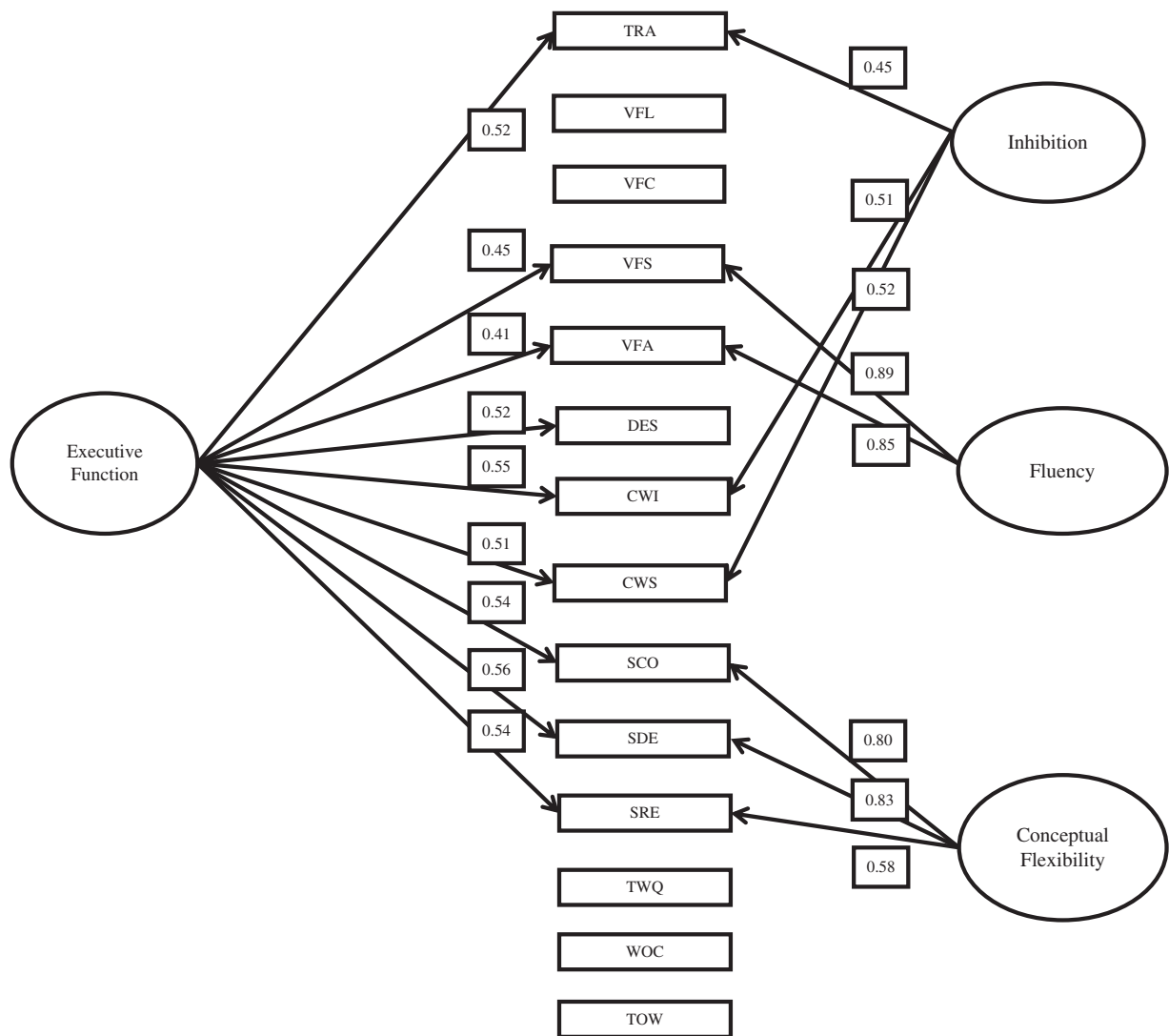
Fig. 1. Bifactor model and factor loadings. Factor loadings above >.40 are shown. TRA = Trail Making; VFL = Verbal Fluency Letters; VFC = Verbal Fluency Category; VFS = Verbal Fluency Switching; VFA = Verbal Fluency Accuracy; DES = Design Fluency; CWI = Color-Word Inhibition; CWS = Color-Word Switching; SCO = Sorting Correct; SDE = Sorting Description; SRE = Sorting Recognition; TWQ = Twenty Questions; WOC = Word Context; TOW = Tower.

conceptual flexibility among carriers of the L/L genotype (B = .94; *SE* = .34; *p* < .01), but not among S/S or S/L individuals (B = − .18; *SE* = .30; *p* = .59). We then examined regions of significance using the Johnson-Neyman method (Preacher, Curran, & Bauer, 2006), revealing that conceptual flexibility scores did not differ between L/L versus S/L and S/S genotype groups at parental supervision *Z*-scores greater than − 1.51. In other words, despite the association with conceptual flexibility as a function of increasing parental supervision, the L/L genotype group had significantly lower scores on conceptual flexibility at very low self-reported levels of parental supervision compared to the S/L and S/S groups. No significant *5-HTTLPR* by parental supervision interactions emerged for the general EF factor (B = − .38; *SE* = .25; *p* = .14) or inhibition (B = − .04; *SE* = .14; *p* = .78), although a marginally significant interaction effect was found for fluency (B = 1.00; *SE* = .57; *p* = .08).

DISCUSSION

As hypothesized, three factors of EF emerged that reflected domains related to conceptual flexibility, inhibition, and fluency. The covariation between EF factors was associated with a single general factor, evidence that EF may be comprised of both unitary and disparate components. There was a significant main effect of *5-HTTLPR* genotype on the general EF factor, such that individuals with the L/L genotype had lower scores on this factor than individuals without this genotype. Additionally, a significant *5-HTTLPR* genotype by parental supervision interaction emerged that was specific to conceptual flexibility, even after controlling for race-ethnicity, sex, parental education, and child age. Specifically, youth with the L/L genotype performed worse on conceptual flexibility given very low levels of parental supervision compared to youth with S/S or S/L genotypes.

Table 3. Hierarchical regression parameter estimates

		Estimate	SE	p	R^2
Executive function	Step 1	—	—	—	.24
(General Factor)	Parental Supervision	.15	.14	.31	—
	5-HTTLPR genotype	**-.55**	**.27**	**.05**	—
	Step 2	—	—	—	.26
	5-HTTLPR × Parental Supervision	−.38	.25	.14	—
Conceptual Flexibility	Step 1	—	—	—	.03
(Factor 1)	Parental Supervision	.29	.26	.27	—
	5-HTTLPR genotype	−.09	.50	.86	—
	Step 2	—	—	—	.08
	5-HTTLPR × Parental Supervision	**−1.18**	**.45**	**<.01**	—
Inhibition	Step 1	—	—	—	.08
(Factor 2)	Parental Supervision	.12	.08	.10	—
	5-HTTLPR genotype	−.17	.15	.24	—
	Step 2	—	—	—	.08
	5-HTTLPR × Parental Supervision	−.04	.14	.78	—
Fluency	Step 1	—	—	—	.01
(Factor 3)	Parental Supervision	−.29	.31	.36	—
	5-HTTLPR genotype	.07	.61	.90	—
	Step 2	—	—	—	.04
	5-HTTLPR × Parental Supervision	1.00	.57	.08	—

Note. Covariates are not presented in the table but were modeled in both steps.

The factor structure of EF is relatively consistent with previous factor analytic studies (e.g., Latzman & Markon, 2010; Lee et al., 2013). During adolescence, distinct factors representing conceptual flexibility, inhibition, and fluency emerged in prior studies, including a general factor that largely accounted for the covariation between these dimensions. However, there is likely to be factorial variance outside of this developmental epoch, particularly in younger children where a two-factor structure has been reported (e.g., Huizinga et al., 2006; van der Sluis, de Jong, & van der Leij, 2007). Over the course of development, particularly from childhood to young adulthood, different neural circuits and brain regions mature along distinct trajectories (Ernst, 2014); the PFC, in particular, is crucial in regulating EF process and its development typically follows a linear trajectory of

maturation as a function of age, such that certain abilities and functions to do not fully come online until adolescence (Ernst, 2014). This may explain why adolescent and adult samples typically converge on three factors of EF, whereas younger samples typically converge on two factors. The PFC may be associated with the general factor of EF, regions within the PFC and other subcortical structures (e.g., striatum, amygdala) may regulate specific dimensions of EF (Ernst, 2014; Monchi, Petrides, Strafella, Worsley, & Doyon, 2006; Stuss & Alexander, 2000; Taylor et al., 2004). Inhibition, conceptual flexibility, and updating were preferentially activated in the posterior regions of the left superior parietal gyrus and right intraparietal sulcus in a neuroimaging study (Collette et al., 2005). Conceptual flexibility was associated with activation in the inferior frontal gyrus (Hirschorn & Thompson-Schill, 2006; Periáñez et al., 2004), whereas inhibition was associated with activation of the right orbitofrontal gyrus (Collette et al., 2005).

We found a main effect of 5-HTTLPR genotype on the EF general factor, whereby individuals with the L/L genotype had lower scores on the EF general factor than individuals without this genotype, again suggesting that 5-HT regulation plays a generally important role in EF (Logue & Gould, 2014). Studies have shown an inverse association between the L allele, which is more transcriptionally active in coding 5-HT transporter proteins compared to the S allele, and performance on conceptual flexibility tasks in humans (Borg et al., 2009; Jedema et al., 2010), rodents (Birrell & Brown, 2000) and nonhuman primates (Clarke, Dalley, Crofts, Robbins, & Roberts, 2004; Lapiz-Bluhm et al., 2008). In addition, dimensions of EF may be influenced by different
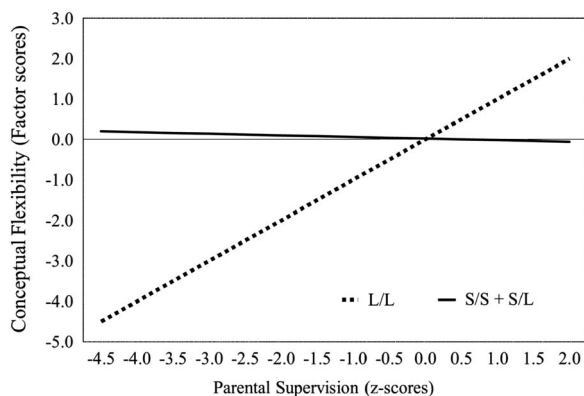

Fig. 2. 5-HTTLPR genotype × parental supervision interaction.

(and overlapping) neurochemical and genetic pathways in the PFC (Anderson, Northam, Hendy, & Wrenall, 2001; Jurado & Roselli, 2007). Genes associated with dopamine receptors and transporters have been linked to performance in response inhibition (Ghahremani et al., 2012; Krämer et al., 2009) and working memory (Bertolino et al., 2006; Blanchard, Chamberlain, Roiser, Robbins, & Müller, 2011). Furthermore, a functional polymorphism in the catechol-O-methyltransferase (*COMT*) gene was associated with sustained attention and conceptual flexibility (Logue & Gould, 2014). These other genetic pathways, not examined here, also warrant consideration.

Previous genetic association studies on EF have largely ignored the potential contribution of environmental influences. We found that the association of *5-HTTLPR* genotype was moderated by parental supervision for conceptual flexibility, but not for fluency or inhibition, and no longer for the EF general factor. Specifically, individuals with the L/L genotype may be more sensitive to parental influences in the context of their cognitive maturation trajectories (Ernst, 2014). Human neuroimaging studies suggest that these associations may be mediated by the distinct neural pathways, whereby environmental stressors may be increase the activation of the amygdala, which in turn relays signals to regulatory circuits in the PFC (see Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Hackman, Farah, & Meaney, 2010). However, the fact that the L allele conveyed increased sensitivity to parental supervision for conceptual flexibility is in contrast to the prevailing GxE literature for *5-HTTLPR* and psychopathology, which consistently show that S allele carriers are more sensitive to environmental influences for internalizing and externalizing phenotypes than individuals carrying the L allele (Gibb et al., 2009; Kaufman et al., 2004; Li & Lee, 2010; Reif et al., 2007; Retz et al., 2008). One explanation is that certain genes are known to be pleiotropic (i.e., genes that effect multiple traits; Chesler et al., 2005) and their associations may differ depending on the phenotype. For example, the *Val/Met* polymorphism in the *COMT* gene was differentially associated with emotion-regulation versus cognitive phenotypes (Mier, Kirsch, & Meyer-Lindenberg, 2010). Similarly, there may also be functional variation in *5-HTTLPR* with respect to emotion versus cognition, such that S allele homozygotes performed better on cognitive tasks but were more vulnerable to depression and anxiety than L allele carriers (Gizer et al., 2009; Wiekum et al., 2013). Allelic functionality may also diverge depending on the environment (Borg et al., 2009), where certain genotypes that were previously believed to confer risk in an adverse environment may also be simultaneously beneficial in the context of an enriched or supportive environment (Belsky & Pluess, 2009). The phenotypic and genetic complexity of EF warrants additional study, as different genetic and environmental influences may be at play for specific dimensions of EF.

Although parental supervision has been well-studied across a variety of developmental phenotypes, including delinquency (Murray & Farrington, 2010) and substance use (Bogenschneider, Wu, Raffaelli, & Tsay, 1998; Clark et al., 2004, 2005, 2008), few studies have focused on parental supervision in the context of EF development. Previous empirical and meta-analytic studies have produced mixed results for parental supervision and academic achievement (Li et al., 2014; Stattin & Kerr, 2000; Weiss & Schwarz, 1996;), which is robustly related to EF abilities (Best, Miller, & Naglieri, 2011; Clark, Prior, & Kinsella, 2002). It is possible that the inconsistency in the literature is due to the relevance of parental influences on EF, which has been understudied. In addition, our findings suggest that parental influences continue to play a crucial role in the development of EF beyond childhood, which is in line with developmental theories (Galambos, Barker, & Almeida, 2003; Steinberg & Silk, 2002). Future studies should explore the association between EF development during adolescence and other aspects of parenting, including support, warmth, and involvement, given previous work showing that these factors are associated with socioemotional and brain development in young children (Conger, Ge, Elder, Lorenz, & Simons, 1994; Tucker-Drob & Harden, 2012).

Several study limitations should be noted. First, our investigation focused on a single aspect of parenting (i.e., parental supervision). Although the importance of parental supervision in relation to adolescent outcomes is well-established, other dimensions of parenting, such as parental warmth, support, and involvement, have also been shown to be associated with EF development in younger populations (Hughes & Ensor, 2009) and may be relevant to cognitive development in adolescents as well. Second, cultural factors may have played a role in the GxE. Although race-ethnicity was statistically controlled in our analyses, *5-HTTLPR* alleles may be nonrandomly distributed by race and ethnicity in much larger populations and may have affected the genetic associations in our study (Gelernter, Cubells, Kidd, Pakstis, & Kidd, 1999). Racial-ethnic differences may also have influenced the magnitude of the association between parental supervision and EF, as one study found that parental supervision was inversely related to academic achievement among Asian Americans students but not with Caucasian students (Mau, 1997). Thus, racial-ethnic issues may be important to address in larger samples. Third, like most candidate gene studies, our sample was underpowered to detect genetic main effects. Genome-wide association studies (GWAS) of psychiatric and behavioral phenotypes have established that individual SNPs convey very small effects individually and account for only a fraction of the overall variance in the phenotype (Plomin, Haworth, & Davis, 2009). Indeed, variation in *5-HTTLPR* genotype may exert only a small effect on conceptual flexibility and EF in general; other genes may potentially be identified using GWAS, which have yet to be conducted for EF. We await future studies of EF that will use more powerful approaches for gene identification. Fourth, our study of EF was limited to measures assessed by the D-KEFS. This precluded us from investigating other salient aspects of EF, such as those that involve decision-making and risk-taking (i.e., "hot" EF; Kerr & Zelazo, 2004). These functions have been implicated in the orbitofrontal cortex (Kerr & Zelazo, 2004), a region in the brain that is also

sensitive to variations in 5-HT and environmental stimuli (Kalin et al., 2008). Additionally, a wider array of measures for EF may potentially uncover a more heterogeneous factor structure for EF than we derived. Finally, the data presented in the current investigation were not assessed longitudinally. Previous longitudinal investigations of EF have established variability in the factor structure of EF as a function of age (Huizinga et al., 2006; Lee et al., 2013; Prencipe et al., 2011; Zelazo et al., 2004). Using longitudinal strategies, such as latent growth curve modeling or structural equation modeling, may allow researchers to examine how genetic influences predict phenotypic patterns over time, while taking into account individual differences in initial status and trajectories. Longitudinal approaches should be prioritized in future investigations of EF.

The current study characterized the latent structure of EF in a typically developing adolescent population with evidence that *5-HTTLPR* genotype interacted with parental supervision in the prediction of conceptual flexibility. Our findings illustrate the utility of using a latent variable framework in the study of complex phenotypes and suggest that the dimensions of EF may be characterized by different genetic and environment pathways. Furthermore, we anticipate that integrated models of EF that incorporate genetic and environmental influences may potentially facilitate the development and implementation of targeted interventions. There is emerging evidence that *5-HTTLPR* genotype may confer differential sensitivity to parenting behaviors, such that genetically susceptible individuals may develop simultaneously better and worse outcomes in the context of positive and negative parenting conditions, respectively (Hankin et al., 2011; Li et al., 2013). Future studies that incorporate gene-environment models may potentially identify populations that are not only at greater risk for developing negative outcomes, but may also benefit the most from interventions (Jaffee & Price, 2007; Brody, Beach, Philibert, Chen, & Murry, 2009).

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