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5-HTTLPR, victimization and ecological executive function of adolescents

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ABSTRACT

Executive function (EF) plays an important role in guiding peer relationship, school performance and behavior control. Children exposed to traumatic environments have been reported to perform poorer in EF tasks. We explored if the relationship between victimization and EF was dependent on the functional variation *5-HTTLPR* in a non-clinical sample of adolescents. Data on demographics, victimization and daily life EF were collected from school students (Han Chinese, $n=2125$). All those reporting executive dysfunction ($n=169$), and classmate controls ($n=208$), were genotyped for the *5-HTTLPR*. It was shown that the number of victimizations associated positively with executive dysfunction (ED). This association was particularly strong in those homozygous for the short allele of *5-HTTLPR*, whilst a statistical *5-HTTLPR* × victimization interaction on ED was found. Our findings suggest that adolescents with a genotype conferring a low 5-HTT activity are more vulnerable to a childhood adversity-associated ED in their daily life.

1. Introduction

Executive function (EF) is an umbrella term for a collection of interrelated processes that are responsible for purposeful, goal-directed and problem-solving behavior (Anderson, 2002; Gioia et al., 2001), and consists of the principle components initiation, inhibition, shifting, planning, organizing, self-monitoring, emotional control and working memory. It plays an important role in guiding peer relationship, school performance and behavior control. EF development is one of the crucial tasks faced by individuals experiencing adolescence, a significant transitional stage from childhood to adulthood (Crone, 2009). The normal development of EF enables individuals to perform appropriately in everyday life, or else they will have difficulties in action or thought control, and then suffer from maladaptive behavior and impaired social skills (Anderson, 2002; Clark et al., 2012; Denham et al., 2012; Morgan and Lilienfeld, 2000).

Previous studies, have suggested that EF tests that assess the individual's daily functioning in the real-world context, so called ecological EF tests, are more sensitive and informative in identifying EF disorders than conventional neuropsychological tests that are well-controlled under lab environments (Gioia et al., 2000, 2010).

A number of studies have evidenced that early adverse experience influences the programming of neurobiological and cognitive development, which involves several brain regions (e.g. prefrontal cortex, PFC) (Bremner, 2003, 2004). PFC is considered as a main brain region controlling the EF, and it is highly sensitive to stress (Arnsten, 2009; Roberts et al., 1998). Several studies indicated that children exposed to traumatic environments perform poorer in different EF tasks, including work memory, problem solving, and inhibition (DePrince et al., 2009; Fishbein et al., 2009; Mezzacappa et al., 2001).

In our previous study, impaired working memory and ecological EF were found among poly-victims of childhood adversity and the more victimization the poorer EF (Liu et al., 2012). However, not all the individuals who have experienced early adversity develop negative EF outcomes. It may to some extent depend on genetic factors. The *5-HTTLPR* is a functional polymorphism in the promoter region of the human serotonin transporter gene. It is a 44 bp insertion or deletion variation, which results in either a long (L) or a short (S) allele, associated with different levels of *5-HTT* expression and serotonin re-uptake. Results from brain imaging studies have shown that *5-HTTLPR* is associated with functions of specific brain regions, such as the amygdala and PFC (Heinz et al., 2004). Previous research has shown a positive association between the S allele and mood and anxiety disorders (Hariri and

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Holmes, 2006).

Depression is often accompanied by cognitive symptoms, such as concentration difficulties, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM). More specifically, impaired working memory, attention, EF and processing speed, measured by using cognitive test batteries, have been reported to be overrepresented in individuals with major depression and dysthymia (Airaksinen et al., 2004; Farrin et al., 2003). Executive dysfunction (ED) has been proposed to precede depression (Christensen et al., 2006). However, several studies have indicated that the S allele is associated with improved cognitive performance, especially EFs in healthy population (Homberg and Lesch, 2011). Roiser et al. (2007) and Borg et al. (2009) found that compared to the L carriers, the S allele carriers performed much better in episodic memory and attention tasks as well as in an EF task-Wisconsin Card Sorting Test. In Enge et al. (2011); Wiłkość et al. (2010) studies, SS carriers showed a more efficient executive control of working memory. Thus, results suggest that *5-HTTLPR* should be considered as a marker for plasticity rather than vulnerability (Belsky et al., 2009). Environmental factors play an important role in the effects of *5-HTTLPR.* The interaction between *5-HTTLPR* and environment risk factors, especially childhood adversity, has been extensively investigated in depression. A meta analysis demonstrated the interaction between childhood adversity and *5-HTTLPR* on depression in adulthood, with the S allele carrying vulnerability (Karg et al., 2011). However, little is known if such an interaction affects depression displayed already in adolescence. No such interaction was found in Japanese children with depression (Tomoda et al., 2013). In a study performed in psychotic disorder patients, a significant interaction between *5-HTTLPR* and childhood trauma on cognitive function was observed in adults, where SS carriers exposed to high levels of childhood trauma show poorer cognitive function than SL/LL carriers (Aas et al., 2012).

We here investigated the relationships between victimization (i.e. the number of childhood adversities), the *5-HTTLPR*, and ecological EF in a healthy adolescent population. We hypothesized that: (1) Poly-victimization is related to ecological executive dysfunction. (2) S allele carriers would show better EF compared with L carriers, and be more sensitive to victimization. (3) S allele carriers would show a sharper trend of decrease on EF by increased number of victimization events.

2. Materials and methods

2.1. Subjects

This cross-sectional study involved individuals recruited from two junior schools in Jinan, the capital city of Shandong Province in China. These two junior schools were selected through convenient sampling. All the adolescents in these two schools ($n=2150$), aged 11–17 years, were invited to participate in the study. The participants ($n=2125$) completed questionnaires on demographics, victimization, EF and other aspects of mental health in a paper–pencil test during school time. Individuals with a history of brain injury were excluded ($n=61$). Next, a nested case-control design was applied. Of the 2125 participants, 169 individuals scored as having executive dysfunction (ED) according to the self-reported version of Behavior Rating Inventory of Executive Function (BRIEF-SR (Guy et al., 2004)). Age- and gender-matched controls ($n=208$) were randomly selected from their classmates. Saliva samples were collected from the 169 with executive dysfunction and the 208 control individuals. All the subjects were Chinese Han.

All study procedures were approved by the ethical committee of school of nursing, Shandong University. Details of the present study were described to all the subjects and their parents. After that, an informed consent was signed by both the adolescent and one parent.

2.2. Questionnaires

BRIEF-SR (Psychological Assessment Resources, Inc.) (Guy et al., 2004) was used to assess the emotional and behavioral manifestations of EF. BRIEF-SR comprises 80 items distributed into eight scales that measure the following eight aspects of EF: inhibition, shifting, emotional control, initiation, working memory, planning, organization of materials and monitoring. The sum score of the first four scales (inhibition, shifting, emotional control, and initiation) is the index BRI (Behavioral Regulation), while the sum score of the other four scales (working memory, planning, organization of materials and monitoring) forms the index MI (Meta cognition). The sum of all 80 item scores (the raw total item score) was converted to *T* score adjusted for age and gender. A *T* score of 65 was considered as 'abnormally elevated', whereas a *T* score between 60 and 64 was regarded as 'mildly elevated' (Gioia, 2000). In this study, individuals with a *T* score ≥ 60 were defined as having ecological executive dysfunction (ED).

Victimization of adolescents were assessed using the Juvenile victimization questionnaire (JVQ). JVQ contains screening questions about 33 offenses experienced during the last 12 months arranged under the 5 modules Conventional Crime, Child Maltreatment, Peer and Sibling Victimization, Sexual Victimization, and Witnessing and Indirect Victimization. In this study, numbers of victimization events, rather than different victimization styles, were studied. Adolescents with a JVQ score of 0 were considered as having no victimization, 1–4 as having mild victimization, 5 or higher as having poly-victimization (Finkelhor et al., 2005).

Social and family demographic factors were assessed by specific questions on (i) single child [yes/no], family structure [core family/single parent family/extended family/reconstituted family/live with grandparents only], how he/she would like to evaluate his/her family financial status[rich/ average/ poor], whether he/she moved or not within the last year[yes/no], house crowded [yes/no], parent smoking [never/occasionally/ everyday/ addicted] and parental alcohol use [often drunk/ not often drunk], the relationship with neighbors [harmony/not harmony].

2.3. Genotyping

Genomic DNA was extracted from saliva samples using Saliva DNA Collection and Extraction Kit (Aidlab Biotechnologies Co., Ltd., Beijing, China).

The *5-HTTLPR* region was amplified using the polymerase chain reaction (PCR) using Taq DNA Polymerase (Thermo Scientific, Thermo Fisher Scientific Inc., Waltham, MA, USA) with forward primer 5′-GGCGTTGCCGCTCTGAATGC-3′ and reverse primer 5′-GAGGGACTGAGCTGGACAACCAC-3′. PCR was conducted in a 25 μL reaction mixture, containing 0.2 μM forward primer, 0.2 μM reverse primer, 2.5 μL 10 × Taq buffer, 0.2 mM dNTP, 2 mM $MgCl_2$, 0.125 U/μL Taq DNA Polymerase and 50–200 ng genomic DNA. Cycling conditions were as follow: denaturation at 95 °C for 3 min, and 38 cycles of amplification (95 °C for 30 s, 62 °C for 30 s, and 72 °C for 45 s), with a final extension of 5 min at 72 °C. The PCR products were separated using 2% agarose gel electrophoresis. Fragment sizes corresponding to the S and L alleles were 484 bp and 528 bp, respectively.

2.4. Statistical analyses

The demographic characteristics were compared using *t*-test for normally distributed quantitative data presented as mean ± SD, and χ^2 or Fisher's exact test for qualitative data, between subjects with ED and controls. Univariate analysis was conducted to explore the relation between victimization, *5-HTTLPR* and EF. Hierarchical logistic regression was performed to estimate the main effects of victimization and genotype, together with possible interactions on ED. In the hierarchical logistic regression, environmental factors were entered in the first step, including victimization and demographic characteristics that differed significantly in previous univariate analyses between the groups ED and controls. Next, *5-HTTLPR* was entered, followed by the *5-HTTLPR**victimization interactions in the last step. In order to be consistent with previous studies, we combined SL and LL as L carriers (Aas et al., 2012; Belsky et al., 2009).

Data were analyzed using the IBM SPSS Statistics 22.0 software (IBM Corporation, Somers, N.Y., USA). All statistical tests were two-sided, with *p* value less than 0.05 regarded as statistically significant. The statistical power to detect association of OR above 1.8–2.0 at $\alpha=0.05$ was >0.8.

3. Results

In total, 169 individuals with executive dysfunction (ED) and 208 controls were studied. The genotype distribution of *5-HTTLPR* did not differ significantly from Hardy–Weinberg equilibrium (ED: $\chi^2(n=163)=1.49$, $p=0.22$; and controls: $\chi^2(n=208)=3.35$, $p=0.07$). Demographic characteristics are presented in Table 1.

No significant differences were detected between ED and controls for the variables age, gender, being single child, family structure, financial status, move house, father's smoking status, or alcohol use of mother. However, housing crowdedness was more frequently reported in the ED group compared with the controls.