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MAOA genotype modulates default mode network deactivation during inhibitory control

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ABSTRACT

It has been demonstrated, in a long line of research, that the low-activity genotype of the monoamine oxidase A (MAOA) gene is associated with aggression. Previous work has linked impaired response inhibition to aggression, but little is known about how this relates to the purported MAOA-aggression relationship in adolescents. Here, we examined how *MAOA* genotype influences neural correlates of inhibitory control in 74 healthy male adolescents using a GoStop and a Go/Nogo task while differentiating between action cancelation and action restraint. Carriers of the low-expressing *MAOA* alleles (MAOA-L) did not show altered brain activation in the prefrontal-subcortical inhibition network relative to carriers of the high-expressing alleles across inhibition conditions. However, they exhibited a more pronounced deactivation during response inhibition in the posterior cingulate cortex (PCC) and precuneus, areas belonging to the default mode network (DMN). Larger DMN suppression in MAOA-L carriers might represent a compensation mechanism for impaired cognitive control.

1. Introduction

Aggressive behaviors are social interactions aimed at inflicting harm on another individual. Aggression is a multidimensional construct; it can be classified in a number of ways, while the most commonly used classification is premeditated versus impulsive aggression. Premeditated aggression is goal-oriented, planned, and usually oriented towards a rewarding or positive outcome. The impulsive aggression is characterized by unplanned, uncontrollable actions, and is often driven by emotional provocation (Parrott & Giancola, 2007; Vitaro & Brendgen, 2011). Impulsive aggression is also called reactive aggression, since it usually refers to a response to a perceived stress. Normally impulsive aggression is adaptive, helping people and animals to be aware of dangers, to guard their homes from intruders and protect themselves and their children from threats. However, impulsive aggression becomes pathological when aggressive responses are out of proportion to the actual stressors (Siever, 2008).

The predisposition to impulsive aggression is deeply rooted in genetics, which has been confirmed by twin and adoption studies (Coccaro, Bergeman, & McClearn, 1993; Coccaro, Bergeman, Kavoussi, & Seroczynski, 1997). The best-validated genetic contributor to impulsive aggression is the monoamine oxidase A (*MAOA)* gene, located on the short arm of the X chromosome (Xp11.4-p11.23) (Grimsby, Lan, Neve, Chen, & Shih, 1990). The *MAOA* gene encodes the monoamine oxidase A enzyme that catalyzes the degradation of monoaminergic neurotransmitters implicated in impulsive aggression, including serotonin, norepinephrine and dopamine (Seo, Patrick, & Kennealy, 2008).

MAOA was first linked to vulnerability for aggression in the 1990s by evidence from human and genetic knock-out mice data (Brunner, Nelen, Breakefield, Ropers, & van Oost, 1993; Cases et al., 1995; Shih & Thompson, 1999). Brunner et al. (1993) reported mental retardation and impulsive aggression in eight men within an extended Dutch family wherein all eight had a common point mutation in the *MAOA* gene. Consistently, *MAOA*-knockout male mice exhibited abnormally high levels of serotonin and norepinephrine together with an increase in offensive aggressive behaviors (Cases et al., 1995). The apparent link between *MAOA* and aggression was confirmed robustly by genetic studies of a polymorphic variant of this gene, namely the upstream

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variable-number tandem repeat (uVNTR) polymorphism, which occurs in five alleles with different numbers (2, 3, 3.5, 4, and 5) of 30-bp repeats 1.2 kb upstream of the *MAOA* transcription initiation site (Sabol, Hu, & Hamer, 1998). The importance of the uVNTR polymorphism in relation to aggression arises from its influence on MAO-A activity, wherein the 2-, 3-, and 5-repeat alleles are associated with lower transcriptional efficiency (MAOA-L) at the *MAOA* promoter than the 3.5- and 4-repeat alleles (MAOA-H), and thus lower MAO-A enzyme activity in the brain (Sabol et al., 1998). Among these, MAOA-L alleles are linked to a high risk for impulsive aggression in a bulk of studies, especially when combined with childhood maltreatment (Caspi et al., 2002; Chester et al., 2015; Kim-Cohen et al., 2006; Kuepper, Grant, Wielpuetz, & Hennig, 2013; McDermott, Tingley, Cowden, Frazzetto, & Johnson, 2009; Oreland, Nilsson, Damberg, & Hallman, 2007; Weder et al., 2009; Widom & Brzustowicz, 2006).

Deficits in inhibitory control have been suggested as a mechanism facilitating impulsive aggression (Feilhauer, Cima, Korebrits, & Kunert, 2012; Pawliczek et al., 2013; Utendale et al., 2014). Therefore, neuroscientists were working to identify the neural correlates of inhibitory control that are probably involved in impulsive aggression in MAOA-L carriers. Passamonti and his colleagues showed that male MAOA-L carriers exhibited decreased activation in ventrolateral prefrontal cortex and ACC during an inhibitory control paradigm (i.e., Go/NoGo task) (Passamonti et al., 2006, 2008), suggesting a prefrontal dysfunction in MAOA-L carriers who have a propensity for impulsive aggression. However, sample sizes of these two studies were relatively small (24 and 35, respectively). Another study based on an American sample showed a sex by genotype interaction on anterior cingulate cortex (ACC) activation during a combined Flanker/GoNogo task, wherein MAOA-L males exhibited attenuated ACC responses during response inhibition compared with MAOA-H males while females did not show a difference in brain activation (Meyer-Lindenberg et al., 2006). In a recent neuroimaging study with a large-sample (N = 125, 72 males), Holz et al. found a sex-specific interaction between *MAOA* genotype and childhood life stress on ACC activity during response inhibition (Holz et al., 2014). They found MAOA-L men showed decreased activation with the level of childhood life stress, while MAOA-H men demonstrated increased brain responses. Taken together, these studies suggest a prefrontal dysfunction during response inhibition in MAOA-L carriers who have a propensity for impulsive aggression.

However, these studies defined inhibitory control as a unitary concept measured with the Go/Nogo task. However, previous research differentiates between different types of inhibitory control (Eagle, Bari, & Robbins, 2008). In this context, “action restraint” is considered as an inhibition process that requires inhibiting the initiation of a motor response when a “nogo” stimulus is presented, for example during a Go/Nogo task. In contrast, “action cancelation” is considered as an inhibition process where an already initiated motor response needs to be inhibited when a stop stimulus is presented shortly after a go stimulus, for example during a Stop-Signal task (SST) (Eagle et al., 2008; Schachar et al., 2007; Swick, Ashley, & Turken, 2011). While comparison of neural correlates of “stopping” and “not going” in a meta-analysis revealed considerable overlap of fronto-subcortical networks during action cancelation and action restraint, we believe that it is important to clarify whether one specific inhibition process is related to the MAOA-L risk genotype.

Additionally, the aforementioned studies only focused on adult samples. Until today, it is not clear yet whether compromised prefrontal functioning during inhibitory control would also affect MAOA-L carriers already in adolescence. Adolescence is a vital period for individual physical and mental development. Adolescents are more prone to risk-taking behaviors like violence, substance abuse and unprotected sexual intercourse (Jiang et al., 2015; Martin et al., 2002; Zhang et al., 2014). One important reason is that in adolescents the ability of impulse control, an essential part of the top-down control systems, is still relatively immature (Casey, Jones, & Hare, 2008). Structural magnetic resonance imaging (MRI) studies suggested that prefrontal areas and some subcortical structures will not mature until early adulthood (Gogtay et al., 2004). This asynchronous brain development, specifically in the prefrontal cortex, is suggested as a neural mechanism underlying the immature top-down control systems in adolescents, and it also indicates a possibility that self-control ability might be trained and improved during this critical period, specifically in at risk populations carrying the MAOA-L genotype.

In the present study, we examined the influence of *MAOA* polymorphisms in a male adolescent sample on neurophysiological correlates of inhibitory control using a functional MRI-adapted version of GoStop task and a pure Go/Nogo task (Dougherty et al., 2003; Li, Wang, Yao, Hu, & Friston, 2012). We focused on male adolescents as our subjects since many aggression-related externalizing behaviors are more serious in this cohort (Card, Stucky, Sawalani, & Little, 2008). Also, *MAOA* is an X-linked gene; girls carry two alleles and thus can have two MAOA-H alleles, two MAOA-L alleles, or one of each. It is thus not clear yet how the *MAOA* genotype determines *MAOA* gene transcription in females (Benjamin, Van Bakel, & Craig, 2000; Carrel & Willard, 2005), preventing inferences about relative MAO-A activity in heterozygous females. Therefore, girls were excluded from this study to minimize potential confounding factors. Neural correlates of action cancelation were assessed with the GoStop task. Additionally, action restraint was measured with the pure Go/Nogo task. This task setup allowed us to test for differential effects of *MAOA* genotype on neural correlates of subtle inhibition processes.

In light of convergent findings implicating impaired functioning in the ventrolateral prefrontal cortex and the ACC during inhibitory control in carriers of the MAOA-L alleles (Holz et al., 2014; Meyer-Lindenberg et al., 2006; Passamonti et al., 2006, 2008), we predicted that MAOA-L individuals would show reduced inhibition-related activation within the aforementioned regions. Furthermore, we aimed to test the importance of brain responses showing differential genotype effects during response inhibition as a neural index in the *MAOA* gene-aggression relationship by assessing correlations with self-reported aggression.

2. Methods

2.1. Participants

Male adolescent participants were selected randomly from a regular senior high school in Changsha, China. The inclusion criteria included normal (or corrected to normal) hearing and vision, an intelligence quotient (IQ) above 80, and no prior DSM-IV psychiatric or emotional disorder. All initially selected participants completed the Wechsler Intelligence Scale for Children-Chinese revision (C-WISC) to examine the IQ (Gong & Cai, 1993), and a Structured Clinical Interview for the DSM-IV-TR Axis I Disorders–Patient Edition (SCID-I/P) (First, 2005) administered by two well-trained experimenters. All participants were ethnic Han Chinese and right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). A cohort of 82 healthy male high-school students was enrolled in this study. All subjects and their parents were made aware of the purpose of the study and provided informed written consent. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Second Xiangya Hospital of Central South University, China.

2.2. MAOA genotyping

Genomic DNA (gDNA) was extracted from venous blood samples with the TIAN amp Blood DNA Kit (TIANGEN Biotech, Beijing, China) according to standard procedures. *MAOA* polymorphisms were identified by polymerase chain reaction assays with a protocol modified from Sabol et al. (1998). The forward primer was 5′-ACA GCC TGA CCG TGG AGA AG-3′ and the reverse primer was 5′-GAA CGG ACG CTC CAT TCG