Understanding Genetic Risk for Aggression: Clues From the Brain's Response to Social Exclusion

Naomi I. Eisenberger, Baldwin M. Way, Shelley E. Taylor, William T. Welch, and Matthew D. Lieberman

Background: Although research indicates a relationship between the monoamine oxidase-A (MAOA) gene and aggression, the intervening neural and psychological mechanisms are unknown. Individuals with the low expression allele (MAOA-L) of a functional polymorphism in the MAOA gene might be prone to aggression because they are socially or emotionally hyposensitive and thus care less about harming others or because they are socially or emotionally hypersensitive and thus respond to negative social experiences with defensively aggressive behavior.

Methods: We investigated the relationships between the MAOA polymorphism, trait aggression, trait interpersonal hypersensitivity, and neural responses to social exclusion in 32 healthy men and women.

Results: The MAOA-L individuals (men and women) reported higher trait aggression than individuals with the high expression allele (MAOA-H). The MAOA-L individuals reported higher trait interpersonal hypersensitivity and showed greater dorsal anterior cingulate cortex (dACC) activity (associated with rejection-related distress) to social exclusion compared with MAOA-H individuals, consistent with a social hypersensitivity hypothesis. Moreover, the MAOA–aggression relationship was mediated by greater dACC reactivity to social exclusion, suggesting that MAOA might relate to aggression through socioemotional hypersensitivity.

Conclusions: These data suggest that the relationship between MAOA and aggression might be due to a heightened rather than a reduced sensitivity to negative socioemotional experiences like social rejection.

Key Words: Aggression, dorsal anterior cingulate cortex, fMRI, interpersonal sensitivity, MAOA gene, MAOA-uVNTR, neuroimaging, social exclusion

In both animal and human populations, aggressive behavior has been linked to a genetic deficiency in monoamine oxidase-A (MAOA), an enzyme that degrades serotonin, dopamine, and norepinephrine (Shih *et al.* 1999). Monoamine oxidase-A–deficient male mice were found to be more aggressive as evidenced by a shorter latency to attack and a greater number of skin wounds in a resident-intruder paradigm (Cases *et al.* 1995). Monoamine oxidase-A–deficient men from a single Dutch kindred demonstrated elevated levels of impulsive aggression, arson, and attempted rape (Brunner *et al.* 1993). In line with these findings, when exposed to early adversity, men with the low expression allele (MAOA-L) of the 30-base pair (bp) variable number tandem repeats polymorphism in the MAOA promoter (MAOA-uVNTR) were more likely to develop antisocial behavior than men with the high expression allele (MAOA-H; Caspi *et al.* 2002). Despite mounting evidence suggesting a relationship between the MAOA-uVNTR polymorphism and aggressive behavior, it is unclear how this genetic polymorphism predisposes individuals to aggressive behavior.

Aggression researchers have distinguished between two types of aggressive behavior, one resulting from a lack of emotional sensitivity and one resulting from excessive emotional sensitivity (Blair *et al.* 2006; Crick and Dodge 1996). Instrumental or proactive aggression is pre-meditated, goal-directed aggression that is used to obtain a desired goal. This type of aggression has been associated with psychopathy and often involves diminished emotional sensitivity, empathy, and remorse (Berkowitz 1993; Blair *et al.* 2006; Frick *et al.* 2003). Reactive aggression, in contrast, is triggered by negative experiences and involves exaggerated levels of negative emotion, such as anger or anxiety, in response. This type of aggression is thought to result from a more responsive threat detection system as well as a diminished capacity to regulate the heightened emotional responses (Blair 2004; Blair *et al.* 2006; Grafman *et al.* 1996). Despite the fact that aggressive behavior clearly relates to affective processes, few neuroimaging studies have investigated how the MAOA polymorphism relates to neural activity associated with these affective processes. Instead, neuroimaging studies have focused primarily on how the MAOA polymorphism relates to executive attention or inhibitory control during cognitive tasks, typically observing that the MAOA polymorphism relates to altered activity in neural regions involved in triggering and instantiating cognitive control (Fan *et al.* 2003; Meyer-Lindenberg *et al.* 2006; Passamonti *et al.* 2006).

To date, only one study has examined the relationship between the MAOA polymorphism and affect-related processing. This study examined how the MAOA polymorphism related to individual differences in the gray matter volume of limbic regions and in the responses of these regions to emotional stimuli, specifically negative emotional faces (Meyer-Lindenberg *et al.* 2006). Compared with MAOA-H, MAOA-L individuals showed reduced gray matter volumes in limbic regions such as the amygdala, dorsal anterior cingulate cortex (dACC), and subgenual ACC and greater amygdala and subgenual ACC activity to negative emotional faces. Although this study represents an advance in understanding how the MAOA-uVNTR polymorphism relates to affective processing, the study did not examine self-reports or behavioral assessments of aggression. Moreover, because the affective stimuli used in this study, namely pictures of negative emotional expressions, are not likely to elicit full-blown emotions, it is difficult to know how the MAOA polymor-

From the Department of Psychiatry & Biobehavioral Sciences (NIE), Cousins Center for Psychoneuroimmunology; and the Department of Psychology (BMW, SET, WTW, MDL), University of California, Los Angeles, California.

Address reprint requests to Naomi I. Eisenberger, M.D., UCLA, Cousins Center for Psychoneuroimmunology, 300 Medical Plaza, Room 3156, Los Angeles, CA 90095-7076; E-mail: neisenbe@ucla.edu.

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phism relates to actual emotional responses to negative events. Thus, in the present study, we examined how the MAOA polymorphism related to trait aggression as well as how it related to neural responses to a negative socioemotional experience that has been shown to elicit real negative feelings, specifically an experimental episode of social exclusion (Williams *et al.* 2000).

In line with the distinction between aggression due to blunted emotional sensitivity (instrumental) versus aggression due to exaggerated emotional sensitivity (reactive), we examined whether MAOA-L individuals showed evidence of social hyposensitivity, making them more likely to commit violent acts because they care less about harming others, or social hypersensitivity, making them more sensitive to negative social events and more likely to respond with defensively aggressive behavior (Dodge and Pettit 2003; Twenge *et al.* 2001). Although each of these possibilities results in aggressive behavior, the experiential predictors of these acts are quite different and would have different implications for treatment alternatives.

We first examined how the MAOA polymorphism related to self-reported trait aggression (e.g., "having urges to harm someone") in both men and women. We then examined whether MAOA-related aggression was associated with social hypo- or social hyper-sensitivity by examining: 1) how the MAOA polymorphism related to self-reported trait interpersonal hypersensitivity (e.g., "you feel that people are unfriendly or dislike you," "your feelings are easily hurt"), and 2) how the MAOA polymorphism related to neural responses to an experimental episode of social exclusion. Previous work has shown that, in response to an experimental episode of social exclusion, participants show increases in self-reported social distress (e.g., "I felt rejected") (Williams *et al.* 2000) and that these increases in social distress parallel increased activity in the dACC (Eisenberger *et al.* 2003). Thus, if the MAOA–aggression link reflects reduced socioemotional sensitivity, MAOA-L individuals should report less trait interpersonal hypersensitivity and show less dACC activity to social rejection than MAOA-H individuals. Alternatively, if the MAOA–aggression link reflects heightened socioemotional sensitivity, MAOA-L individuals should report greater trait interpersonal hypersensitivity and show greater dACC activity to social rejection than MAOA-H individuals. In either case, MAOA-L individuals should report higher levels of trait aggression than MAOA-H individuals.

Methods and Materials

Subjects

Members of the University of California at Los Angeles (UCLA) community responded to an advertisement offering $60 for participation. Prospective participants with the following conditions were excluded from participation through a structured telephone interview: serious physical or mental health problems (e.g., "Has a doctor ever told you that you have a serious physical/mental health problem?"), current treatment from a mental health professional, current use of mental health-related medication (e.g., Prozac), claustrophobia, and the presence of metals in their bodies (dental fillings were allowed). Thirty-two healthy, right-handed participants (19 female; mean age = 20.59, SD = 3.17) provided written informed consent. The sample was 28.1% European-American, 40.6% Asian, 15.6% Hispanic, 6.3% African-American, and 9.4% "mixed" or other, a pattern that reflects the composition of the UCLA community. Experimental procedures were approved by the UCLA Human Subjects Protection Committee.

Measures

Before completing the neuroimaging task, participants completed several self-report measures related to aggression and interpersonal hypersensitivity. Specifically, participants completed the Brief Symptom Inventory (BSI) (Derogatis and Spencer 1982), which contains a subscale assessing hostility (e.g., "How bothered do you feel about: ". . . having urges to beat, injure, or harm someone?" ". . . feeling easily annoyed or irritated?") and a subscale assessing interpersonal hypersensitivity (e.g., "How bothered do you feel about: ". . . feeling very self-conscious with others?" ". . . your feelings being easily hurt?"). Both of these subscales demonstrated strong reliability (hostility subscale: $\alpha = .76$; interpersonal hypersensitivity subscale: $\alpha = .85$). Participants also completed the Spielberger Trait Anger scale (Spielberger *et al.* 1985; e.g., "When I get frustrated, I feel like hitting someone," "When I get mad, I say nasty things"). This measure also demonstrated strong reliability ($\alpha = .83$). Trait aggression scores were calculated by normalizing and then averaging scores from the hostility subscale of the BSI and the Spielberger Trait Anger scale. Interpersonal hypersensitivity scores were calculated by taking the average of the items in the BSI interpersonal hypersensitivity subscale.

Genotyping

After the completion of the self-report measures, DNA was obtained with the Orasure oral specimen collection device (Orasure Technologies, Bethlehem, Pennsylvania) and extracted with the Puregene DNA purification kit (Gentra Systems, Minneapolis, Minnesota). The MAOA-uVNTR polymorphism was identified using polymerase chain reaction (PCR) with a protocol modified from Sabol *et al.* (1998). The forward primer was 5'-ACA GCC TGA CCG TGG AGA AG-3' (VIC labeled [Applied Biosystems, Foster City, California]) and the reverse primer was 5'-GAA CGG ACG CTC CAT TCG GA-3'. Amplification was performed in a total volume of 8 μL containing 25 ng DNA, 125 μmol/L primers, 200 μmol/L deoxyribonucleotide triphosphate (dNTP), 10% dimethyl sulfoxide (DMSO), 2.5 mmol/L magnesium dichloride, and .8 U of Amplitaq Gold (Applied Biosystems) in the manufacturer's buffer. Samples were denatured at 94°C for 12 min, followed by 35 cycles of 94°C for 30 sec, 55°C for 30 sec, and 72°C for 2 min. The PCR products were separated on an ABI 3700 DNA analyzer (Applied Biosystems). To assess genotyping accuracy, 15 samples were reprocessed, and no errors were detected. Alleles were grouped into either a low expression category that consisted of 2, 3, and 5 repeats of the 30-bp sequence or a high expression category that consisted of a 4-repeat allele as well as 3-repeat allele with an additional 18-bp incomplete repeat, as performed previously (Caspi *et al.* 2002; Meyer-Lindenberg *et al.* 2006; Sabol *et al.* 1998).

Because MAOA is an X-linked gene, men carry only one allele and can thus only be MAOA-L or MAOA-H; however, women carry two alleles and can thus have two MAOA-L alleles, two MAOA-H alleles, or one of each. Thus, there were three genotype categories: 1) the MAOA-L category ($n = 13$), consisting of men with MAOA-L and women with two copies of MAOA-L, 2) the MAOA-LH category ($n = 10$), consisting of women with one copy of MAOA-L and one copy of MAOA-H, and 3) the MAOA-H category ($n = 9$), consisting of men with MAOA-H and women with two copies of MAOA-H. Previous research has shown that female heterozygotes show patterns of neural