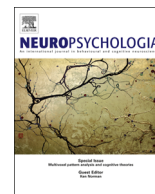




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Mental rotation in intellectually gifted boys is affected by the androgen receptor CAG repeat polymorphism



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ABSTRACT

Testosterone was shown to organize brain and modulate cognitive functions. It is currently unknown whether mental rotation is also associated with prenatal testosterone exposure and testosterone-related genetic polymorphisms. The aim of our study was to analyze associations between mental rotation performance, the actual testosterone levels, the prenatal testosterone level (expressed as 2D:4D ratio) and the androgen receptor CAG repeat polymorphism in intellectually gifted boys. One hundred forty-seven boys aged 10–18 years with IQ > 130 were enrolled. Saliva samples were collected and used for ELISA of actual levels of salivary testosterone. The 2D:4D finger length ratio as an indicator of prenatal testosterone was measured on both hands and averaged. Amthauer mental rotation test was used for the assessment of this spatial ability. The CAG repeat polymorphism in the androgen receptor gene was analyzed using PCR and capillary electrophoresis. Linear regression revealed that 2D:4D finger length ratio and the number of CAG repeats in the androgen receptor gene were associated with mental rotation. Actual levels of testosterone did not correlate significantly with mental rotation. Multivariate analysis of covariance revealed that after adjustment of age as a confounding variable, only the effect of the genetic polymorphism was significant. The results are in line with our previous genetic analysis of intellectually gifted boys showing the importance of CAG repeat polymorphism in the androgen receptor gene. Details of the interactions between androgen signaling, testosterone levels and its metabolism especially during the prenatal development of brain function remain to be elucidated.

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1. Introduction

Individuals classified as “gifted” display a unique set of abilities, talents and skills leading to extraordinary accomplishment often from an early age (Mrazik & Dombrowski, 2010). There are several unique neurobiological features present in the majority of gifted children supporting the connection between extraordinary intelligence and brain pattern development.

Specifically, there is a trend toward increased right-hemisphere involvement in this population. Geschwind–Behan–Galaburda theory of cerebral dominance argued that higher than normal concentrations of testosterone *in utero* may inhibit aspects of the brain development (typically aspects of left-hemisphere

functioning) while enhancing other areas (typically right-brain development) (Geschwind & Galaburda, 1987). The consequence of this developmental misbalance is the ability to visualize the problems individuals working on and then to translate those visual images into the abstract language of mathematics. According to the callosal theory, prenatal testosterone mediates early axon pruning in callosal tissue, and thus the more testosterone a brain is exposed to prenatally, the more lateralized the brain of individual is (Witelson & Nowakowski, 1991; Ypsilanti, Ganou, Koidou, & Grouios, 2008).

Mental rotation is often said to be right hemisphere function. The evidence is still equivocal, however, some studies found a bilateral network involved in mental rotation tasks. In parietal cortex the activity seems to be more consistently observed in the right hemisphere (Kalmady et al., 2013; Milivojevic, Hamm, & Corballis, 2009; Zacks, 2008).

Possible relationships between early androgens exposure and human spatial abilities have also motivated digit ratio studies. It

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has been proposed that the ratio of the second to fourth digit (2D:4D) may be a proxy of prenatal androgen exposure, such that low 2D:4D ratio is associated with high prenatal androgen exposure (Beaton, Rudling, Kissling, Taurines, & Thome, 2011; Manning et al., 2000; Manning & Fink, 2008; Manning & Robinson, 2003; Manning, Scutt, Wilson, & Lewis-Jones, 1998). Multiple studies have utilized this morphological marker to examine a possible effect of early androgens on spatial ability (Breedlove, 2010; Nowak & Moffat, 2011; Puts, McDaniel, Jordan, & Breedlove, 2008). Some of them have found that these proxy measures of prenatal androgens predict spatial ability, others have found no significant relationship (Berenbaum, Bryk, Nowak, Quigley, & Moffat, 2009; Puts et al., 2008; Sanders, Bereczkei, Csatho, & Manning, 2005; van Anders & Hampson, 2005; van Anders, Vernon, & Wilbur, 2006). Regardless of mixed results in previous studies, digit ratio is still the best available retrospective marker of average differences in prenatal androgen stimulation.

Key support for the view that 2D:4D reflects fetal testosterone is the finding that the magnitude of 2D:4D covaries with a polymorphic repeat CAG sequence in exon 1 of the gene coding the androgen receptor, AR (Ding, Xu, Menon, Reddy, & Barrack, 2004). However, other studies did not find any relationship between polymorphism in AR and the digit ratio (Hurd, Vaillancourt, & Dinsdale, 2011). Genetic variability in AR seems to be another interesting parameter to analyze in order to understand testosterone effect on brain organization. Several studies examined the association between CAG polymorphism and cognitive abilities. In the range of normal variation low number of CAG repeats cause higher transactivation activity of receptor and, thus, higher sensitivity to androgens (Greenland, Beilin, Castro, Varghese, & Zajac, 2004; Irvine et al., 2000). Lee with colleagues found no association between CAG repeat length and fluid intelligence in older men (Lee et al., 2010). Our previous study revealed significant lower number of CAG repeats in the AR gene in gifted boys comparing to controls, indicating stronger androgen signaling in this population. But in this study number of CAG repeats was not correlated with any cognitive skills (Celec et al., 2013).

Even though some authors argue that contribution of androgens to human performance on mental rotation tasks may be limited to earlier, organizational periods (Courvoisier et al., 2013; Puts et al., 2010), there is some evidence supporting the existence of the association between testosterone levels and mental rotation performance (Alexander & Son, 2007; O'Connor, Archer, Hair, & Wu, 2001). Some studies have reported a positive relationship (the higher the testosterone level, the higher the performance) (Hausmann, Schoofs, Rosenthal, & Jordan, 2009), whereas others have found the relationship to follow an inverted U-shape, with best performance occurring when testosterone is neither too low nor too high (O'Connor et al., 2001) or found a negative relationship (Vuoksima, Kaprio, Eriksson, & Rose, 2012). Our previous studies showed significantly lower salivary testosterone levels in intellectually gifted compared to control prepubertal population (Ostatnikova et al., 2007). It would be interesting to show if there is any possible correlation between actual salivary testosterone levels and mental rotation performance in the specific group of gifted children.

The aim of this paper was to reveal correlation between mental rotation performance, the actual testosterone levels, the prenatal testosterone level (expressed as 2D:4D ratio) and AR CAG repeat polymorphism in intellectually gifted boys. We speculate that differential levels of prenatal testosterone exposure cause atypical cerebral laterality in individuals that should be evident in lower 2D:4D. Since salivary testosterone has been showed to be lower in gifted boys in comparison with control population, it can be assumed that there is a strong sensitivity of androgen receptor

in postnatal life. Therefore we conducted the analysis of 2D:4D ratio in population of gifted children assuming higher testosterone exposure expressed as lower 2D:4D will be correlated with higher score in mental rotation. We also tried to reveal possible correlation between salivary testosterone levels that tend to be lower in gifted boys, and mental rotation performance. Since the relationship between number of CAG repeats in AR gene and cognitive abilities remains unclear, this study tries to examine the possible association between CAG repeat lengths and mental rotation. We believe that this paper will help partially explain the effect of testosterone on mental rotation.

2. Methods

2.1. Probands

One hundred and forty-seven intellectually gifted boys between 10 and 18 years of age were enrolled in our study. Boys were attending the special school for intellectually gifted learners founded in Bratislava, Slovakia in 1998. Admission criterion for being accepted to this kind of special school was general intelligence score of IQ 130 and more. The conventional wisdom about sex differences in IQ is that males and females have the same average IQ. It is stipulated that males are more variable than females, meaning that there are more mentally deficient and gifted males than females (Fink, Neave, & Manning, 2003). In order to avoid differences due to the gender and have homogeneous group of probands, only boys were enrolled in this study.

Probands and their parents were instructed, informed about the concept of the study and signed the inform consent. All procedures were approved by Ethical Committee of Faculty of Medicine. Probands were requested to collect the whole saliva samples into sterile tube (Sarstedt, Nümbrecht, Germany) between 8:00 and 10:00 am in respect of the circadian rhythm of testosterone. All volunteers will be kindly requested not to eat, drink or wash teeth 30 min before collection procedure.

2.2. Psychological examination

General intellectual ability was assessed by standardized general Wechsler Intelligence Scale for Children, 3rd ed. (WISC-III). The complete test assessing general intelligence was administered and evaluated by trained professional psychologist individually to each child. Performance and verbal scores were determined separately besides the complete assessment. For the psychological evaluation of spatial ability, standard psychological tests were used. Mental rotation scores of our subjects were assessed with paper-and-pencil Slovak language version of the Cube Comparison subtest of the Intelligence Structure Battery (Amthauer, 1993). Subjects were instructed to rotate mentally the cubes with different sites and compare it to four differently designed cubes and one identical rotated cube. The task was to find the target cube in rotated position. The assessment involved 20 tasks and 9 min were allowed for the test. Coefficient K was calculated according to the formula: $K = \frac{\Psi^2}{\rho \times \omega}$; where Ψ is the number of correct answers, ρ is the number of answered tasks and ω is the total number of tasks.

2.3. Genetic analyses

Genomic DNA from saliva was extracted using the silica membrane based kit (Qiagen, Hilden, Germany) following the manufacturer's instructions (QIAamp DNA Blood Mini Kit Handbook 04/2010) according to DNA purification protocol for blood/body fluids. The (CAG) n repeat polymorphism in exon 1 of the androgen receptor gene was amplified using PCR in 20 μ l reaction volume with 250 nmol/L primers: forward: 5' GCGCGAAGTGATCCAGAAC 3' tagged with 6-carboxyfluorescein and reverse 5' CTCATCCAGGACCAGGTAGC 3'; 1 \times Taq buffer (Fermentas, Vilnius, Lithuania) and 1 U of Taq DNA polymerase (Fermentas, Vilnius, Lithuania). The following PCR program was used: initial denaturation step at 94 °C for 4 min, followed by 35 cycles each consisting of denaturation at 94 °C for 45 s, annealing at 59.5 °C for 45 s and polymerization at 72 °C for 45 s. The length of the final fragment was 181 bp. The number of repeats was analyzed by capillary electrophoresis.

2.4. Salivary testosterone

ELISA assay using commercial Salivary Testosterone ELISA kit was used according to manufacturer's instructions (DRG Instruments GmbH, Marburg, Germany). The intraassay coefficient of variation was 4.3% and interassay 7.2%.

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