Neuropsychologia ▮ (▮▮▮▮) ▮▮▮–▮▮▮

Contents lists available at SciVerse ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Hand preference in humans is associated with testosterone levels and androgen receptor gene polymorphism

Elizabeth Hampson [a,b,*], Janani S. Sankar [a]

[a] Department of Psychology, University of Western Ontario, London, ON, Canada N6A 5C2
[b] Graduate Program in Neuroscience, University of Western Ontario, London, ON, Canada N6A 5C2

ARTICLE INFO

Article history:
Received 5 November 2011
Received in revised form
23 March 2012
Accepted 27 April 2012

Keywords:
Handedness
Testosterone
Androgen receptor
Polyglutamine repeat
X-linkage

ABSTRACT

Exposure of the central nervous system to androgens during the early developmental period has been proposed to play a role in the establishment of hand preference in males. Existing data, however, are inconclusive. In the present investigation, handedness was assessed in a large sample of left-, mixed-, and right-handed men ($N=180$) using a standardized handedness inventory. Saliva sampling was used to assay levels of bioavailable testosterone and DNA genotyping was carried out to quantify *AR*-CAG repeat length, a genetic marker of the capacity of the androgen receptor to respond to testosterone. Strongly left-handed males were found to have lower levels of bioavailable testosterone than right-handed males, while males with mixed handedness exhibited a weaker androgen receptor, but no significant difference from right-handers in circulating testosterone levels. These findings support the view that testosterone could play a role in the development of hand preference in males. Furthermore, because the *AR* gene lies on the X chromosome, it provides a potential theoretical bridge to genetic theories of handedness that postulate the existence of an X-linked locus important in the establishment of hand preference.

1. Introduction

Departure from uniform right-hand preference occurs in about 12% of males and 8–10% of females (Gilbert & Wysocki, 1992; McManus & Bryden, 1992; Papadatou-Pastou, Martin, Munafò, & Jones, 2008) and can be expressed as either a weak or strong preference for the contralateral hand. Only a small percentage of individuals choose the left hand consistently to perform a range of everyday actions (Annett, 2004); the majority of non-right-handers show a mixed pattern, reliably using the right hand for some activities and the left for others, and are said to have weak or 'mixed' hand preference. Conceptually, some theorists regard handedness as fundamentally binary, recognizing only right or non-right preference, but mixed handers comprise a distinct and important group in other classification schemes, including some genetic models (Annett, 1985). Non-right-handedness not only constitutes a visible external asymmetry, but also is associated with departure from the norm in other components of cerebral lateralization including language (Rasmussen & Milner, 1977; Knecht et al., 2000), and thus may be representative of a broader pattern of changes in neural architecture.

The early fetal environment and genetic factors both contribute to phenotypic variation in hand preference. In a few individuals, increased preference for the left hand may arise due to developmental instability (Yeo, Gangestad, & Daniel, 1993) or as a pathological consequence of obstetric complications or early cerebral insult (Rasmussen & Milner, 1977; Bakan, Dibb, & Reed, 1973). Patterns of handedness within family pedigrees, however, suggest a heritable component. Early genetic models proposed that variation in handedness could be explained by allelic variation at a single, unspecified, autosomal locus (Annett, 1985; McManus, 1985). According to the 'right shift' model (Annett, 1985) two alternative alleles exist, one that induces the development of speech in the left hemisphere and creates a right-hand bias, and another allele that results in no systematic bias, so that in persons who lack the 'right shift' allele, direction of handedness depends exclusively upon chance influences. Heterozygosity was proposed to result in an intermediate phenotype. McManus (1985) invoked a single gene in which individuals inherited either a 'dextral' allele that, in homozygotes, resulted in obligatory right-handedness or a 'chance' allele that exerts no genetic control over lateralization. The McManus model has been refined to incorporate an additional modifier locus, hypothetically situated on the X chromosome (McManus & Bryden, 1992), enabling the model to explain the maternal effect—the fact that left-handed mothers have more left-handed offspring than do left-handed fathers. A recent model by Jones and Martin (2000) has gone further

* Corresponding author at: Department of Psychology, University of Western Ontario, London, ON, Canada N6A 5C2. Tel.: +1 519 661 2111x84675; fax: +1 519 661 3961.
E-mail address: ehampson@uwo.ca (E. Hampson).

0028-3932/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neuropsychologia.2012.04.027

and argued that the existence of a single X-linked recessive gene with low penetrance can successfully model the distribution of left-handedness observed in a variety of genetic studies, and might in fact constitute the primary site that underlies individual variation in handedness phenotype.

Controversially, the gonadal hormone testosterone has been proposed as an etiological factor that may contribute to the development of hand preference. An influential model by Geschwind and Galaburda (1987) was the first to propose that elevated levels of testosterone during gestation might predispose a fetus to left-handedness and attenuate left-hemisphere language dominance by inhibiting growth in cortical regions of the left hemisphere. Evidence for this hypothesis is limited (Bryden, McManus, & Bulman-Fleming, 1994). However, an alternative model, which argues that *lowered* prenatal testosterone exposure may contribute to non-right-handedness, at least in males (Witelson, 1991), has received qualified support.

The 'Witelson hypothesis' originally was proposed to explain differences between right-handed and nonright-handed men observed in posterior segments of the corpus callosum (Witelson & Goldsmith, 1991). Evidence for an effect of testosterone on handedness has been inconsistent, and is complicated by the ethical inability to manipulate testosterone levels in humans. In agreement with Witelson's hypothesis, however, men with clinical conditions characterized by low testosterone during early development or men suspected to have lower prenatal exposure show an increased prevalence of non-right-handedness (Netley & Rovet, 1984; for review see Lalumière, Blanchard, & Zucker, 2000). Free testosterone levels in the umbilical artery of newborns were found to be higher in right- than left-handers as judged by asymmetry in the grasp reflex (Tan & Tan, 2001). A group difference in testosterone may continue at later developmental stages. Non-right-handedness has been associated empirically with slower rates of pubertal maturation (Coren, Searleman, & Porac, 1986) and quantitatively lower levels of testosterone in adult males (Moffat & Hampson, 1996) and adult females (Moffat & Hampson, 1996; Gadea, Gómez, González-Bono, Salvador, & Espert, 2003), relative to matched groups of right-handers. Some findings, however, imply that heterogeneity may exist within the non-right-handed population with respect to testosterone (Moffat & Hampson, 2000; Gadea et al., 2003). Only one study, by Grimshaw, Bryden, & Finegan (1995), has measured testosterone in amniotic fluid directly. Higher prenatal testosterone at 16 weeks gestational age was associated with stronger right-handedness assessed at age 10, although this finding was in girls not boys. In rhesus macaques, the experimental manipulation of testosterone in the neonatal period was found to alter hand use during visually-guided reaching, with animals exposed neonatally to supraphysiological levels of testosterone showing stronger dependence on the preferred hand as adults relative to control males (Drea, Wallen, & Akinbami, 1995). In free-ranging macaques, Westergaard, Chavanne, Lussier, Suomi, & Higley (2000) found a positive correlation between endogenous testosterone measured at adolescence and frequency of right- versus left-hand use. Not all evidence implicating testosterone is consistent with lower testosterone levels in non-right-handers, however. Significantly, increased left-hand dependence has been reported in patients with congenital adrenal hyperplasia, who are exposed to raised not lowered androgens during prenatal gestation (Nass et al., 1987; Kelso, Nicholls, Warne, & Zacharin, 2000; but see Helleday, Siwers, Ritzén, Hugdahl, 1994; Mathews et al., 2004).

To summarize, several models have proposed that alterations in the exposure of the developing brain to testosterone during the prenatal period are involved in the ontogenesis of left-hand preference (Geschwind & Galaburda, 1987; Witelson, 1991). However, the exact role of testosterone, if any, and even the direction of its effect, are unresolved, as is the persistence of group differences in testosterone at later stages of development.

As part of a larger investigation of androgen markers, cognition, and affect, we recently studied associations between testosterone and hand preference in a large group of adult men who underwent genotyping of the androgen receptor gene, *AR*. A distinctive polymorphism, namely the length of a polyglutamine (CAG) repeat sequence in exon 1 of the *AR* gene, is known to correlate inversely with the activity of the receptor; a longer CAG repeat expansion is associated with lower transcriptional activity and thus with a reduced biological response to testosterone (Zitzmann, 2009). In humans and other primates, testosterone is believed to exert its actions on brain development via the androgen receptor (Breedlove & Hampson, 2002). Thus the effective level of testosterone activity in the fetus is a function not only of the levels of testosterone that are present, but also of variations in fetal *AR* genotype. Of significant interest in light of the genetic models described above, the gene that encodes the androgen receptor resides on the X chromosome.

The current study was undertaken to determine whether right-handed and non-right-handed individuals might differ in testosterone levels or *AR* genotype.

2. Material and methods

2.1. Participants

Participants were 180 physically healthy male volunteers recruited from the University of Western Ontario. Mean age was 18.89 (SD=1.98) years. All participants were free of neurological or endocrine pathology and were screened for medication use by asking them to list, at the end of testing, any medications they were taking on a confidential health questionnaire. Participants were excluded if they reported a medical condition or used any medication that may potentially influence testosterone metabolism or artificially alter testosterone levels (e.g., certain antibiotics or SSRIs). Participants were of normal range bodyweight and received monetary compensation or undergraduate course credit for their participation.

2.2. Procedure

Specimen collection and the assessment of hand preference were conducted individually and took place between 1300 and 1900 h to control for circadian variation in testosterone release. Testosterone concentrations are most steady in the afternoon and early evening (Gupta, Lindemulder, & Sathyan, 2000). Specimen collection during this interval is recommended for studies where individual differences in testosterone are the focus of investigation (Yang, Hooven, Boynes, Gray, & Pope, 2007).

In order to ensure purity of the saliva, participants abstained from eating, drinking fluids other than water, smoking, chewing gum, or brushing their teeth for 30 min prior to sample collection. Upon arrival, DNA was sampled to determine *AR* genotype (CAG repeat length). Saliva was used to quantify testosterone because, unlike serum or plasma, it provides a direct index of the testosterone that is bioavailable (i.e., the fraction that is able to interact with tissue to exert metabolic effects; Pardridge & Demers, 1991; Sannikka, Terho, Suominen, & Santi, 1983; Wang, Plymate, Nieschlag, & Paulsen, 1981). Approximately 45% of the total testosterone in plasma is inert by virtue of binding to sex hormone binding globulin (Dunn, Nisula, & Rodbard, 1981; Griffin & Wilson, 2003). Salivary testosterone derives from the free and albumin-bound fractions. For the measurement of testosterone, one saliva specimen was collected immediately following DNA sampling, while a second was collected approximately 1.25 h later. Testosterone concentrations from the two specimens were averaged. In order to increase the number of left-handers, an additional 25 males were recruited at a later date, and in this subset only a single saliva specimen was available for the measurement of testosterone. This subgroup did not differ significantly from the original group in testosterone levels or *AR* genotype based on matched comparisons controlling for handedness. Providing sampling conditions are adequately controlled, an excellent correlation exists (r=0.85) between a single timepoint measure of testosterone in adults and the mean of seven samples collected over a one year period (Vermeulen & Verdonck, 1992) or periods as long as 10 years (Mazur & Michalek, 1998).

2.2.1. Handedness

Handedness was assessed using a modified version of the Crovitz–Zener Handedness Inventory (Crovitz & Zener, 1962). The Crovitz, along with inventories

Please cite this article as: Hampson, E., & Sankar, J. S. Hand preference in humans is associated with testosterone levels and androgen receptor gene polymorphism. *Neuropsychologia* (2012), http://dx.doi.org/10.1016/j.neuropsychologia.2012.04.027