

Sex differences in digit ratio (2D:4D) are disrupted in adolescents with schizotypal personality disorder: Altered prenatal gonadal hormone levels as a risk factor[☆]

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Abstract

The 2nd to 4th finger digit ratio (2D:4D) is a sexually dimorphic feature determined during gestation indexing prenatal androgen/estrogen levels. More ‘feminized’ 2D:4D phenotype has been demonstrated in schizophrenia versus same-sex controls. This study examined 2D:4D in adolescents with schizotypal personality disorder (SPD). Among normal controls, right 2D:4D was significantly greater (more feminized) in females than males. We replicated laterality effects; significant sex differences only on right. There were no significant sex differences among SPDs. Diagnostic group differences were restricted to White/Caucasian males with greater right 2D:4D in SPDs. Findings suggest disruptions in prenatal gonadal hormones in vulnerability for schizophrenia.

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1. Introduction

Schizophrenia is increasingly conceptualized as a neurodevelopmental disorder with fetal central nervous system perturbations at its origin (McNeil and Cantor-Graae, 2000; Schiffman et al., 2004; Walker et al., 1994; Walker and Diforio, 1997; Weinstein et al., 1999). Some prenatal disruptions linked with schizophrenia (Matsu-

moto et al., 2001) are marked by sex differences. This is consistent with sex differences observed in clinical manifestation/course (Goldstein and Walder, 2006; Walker et al., 2002). Gonadal hormones have both ‘permanent’ organizational effects during fetal brain development and lifelong ‘transient’ activational effects. Disruptions in prenatal gonadal hormones have been implicated in a variety of conditions such as autism and immune dysfunction (Manning et al., 2001; Manning and Bundred, 2000). Specifically, recent findings support a low 2D:4D in children with autism (Milne et al., 2006).

Finger digit ratio, the ratio between 2nd (index) and 4th (ring) digit lengths (2D:4D), is a normally sexually

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dimorphic anatomic trait (males < females; George, 1930) determined by the 14th gestational week, and relatively stable throughout development (Brown et al., 2002; McIntyre et al., 2005; Trivers et al., 2006). 2D:4D is assumed to be an ‘indicator’ of circulating prenatal gonadal hormones; smaller ratio reflects higher fetal testosterone and lower fetal estrogen. This suggestion that 2D:4D is a correlate of prenatal testosterone and estrogen was first made by Manning et al. (1998). Evidence also suggests lateralized 2D:4D sex differences (right > left) indicating greater right sensitivity to fetal androgens (Williams et al., 2000).

2D:4D is correlated with behavioral characteristics. Females with more masculine (i.e., smaller) 2D:4D pattern demonstrate less feminine sex role identity (Csathó et al., 2003). Males with more masculine 2D:4D have higher trait physical aggression (Bailey and Hurd, 2005). One study showed that female homosexual orientation was linked with ‘hyper-androgenized’ 2D:4D (Williams et al., 2000).

There is a relationship between 2D:4D and psychopathology. Children with autism manifest lower 2D:4D ratios than population norms (Manning et al., 2001). In contrast, Arato et al. (2004) showed a more ‘feminized’ (i.e., larger) 2D:4D bilaterally in male and female schizophrenia patients compared to same-sex controls (Arato et al., 2004). Authors deduced that low fetal androgen/estrogen ratio may predispose to schizophrenia, and endocrine factors may be involved in disturbed hemispheric lateralization (Arato et al., 2004). Another study showed female schizophrenia patients had shorter second digit lengths than female controls, with no difference among males, interpreted as a protective effect of prenatal estrogen in females (Procopio et al., 2005).

To date, it is unknown whether the normative pattern of 2D:4D sexual differentiation holds among individuals at high-risk for schizophrenia. Therefore, this study examined sex differences in 2D:4D among adolescents with schizotypal personality disorder (SPD). Identification of abnormalities may elucidate etiologic processes and aid in the identification of individuals at risk.

Based on previous findings, it was predicted that: 1) among normal (NC) adolescents, 2D:4D would be greater in females and 2) male and female SPD adolescents would show a more feminized (larger) 2D:4D than same-sex controls.

2. Method

Subjects were 34 (22 M/12 F) adolescents with a DSM-IV diagnosis of SPD (mean age=14.09 years, S.D.=1.69) and 44 (27 M/17 F) NC adolescents with

no DSM-IV Axis II disorder (mean age=14.20 years, S.D.=1.94). The two groups were comparable within-sex on age (females: $t(27)=1.544$, $p=.134$; males: $t(47)=-0.978$, $p=0.333$). There were no significant diagnostic group differences in race/ethnicity (Pearson $\chi^2=4.361$, $p=0.225$): 1) SPD: 70.6% White/Caucasian ($n=24$), 26.5% African-American ($n=9$), 2.9% Asian-American ($n=1$), 0% other; 2) NC: 54.5% White/Caucasian ($n=24$), 43.2% African-American ($n=19$), 0% Asian-American ($n=0$), 2.3% other ($n=1$). Structured Interview for DSM-IV Personality (SIDP-IV; Pfohl et al., 1997) was administered to all participants.

Following complete study description, participants provided consent in addition to parental written informed consent. Finger digit measurements (nearest 1.0 mm using a ruler) were derived from handprints using a procedure developed by George (1930), which involves measuring the distance between: 1) tip of middle finger to tip of index finger (2D) and 2) tip of middle finger to tip of ring finger (4D), bilaterally. 2D:4D was calculated by dividing 2D by 4D, producing a 2D:4D value *inverse* of the ratio often reported in the literature. This was because handprints were used rather than direct measurement of finger length. We took the mathematical inverse of this ratio (multiplied ratio by -1) to coincide with directional differences in other reports. Thus in our final measure, males tend to have a lower (in this case more negative) ratio than females.

Univariate ANOVA was employed to assess interaction effects of sex by diagnostic group. Because small sample size limits power/sensitivity to detect interaction effects, independent samples t -tests were employed to test for sex and diagnostic group differences in 2D:4D. Given the directional nature of the hypotheses, one-tailed tests were used. Pearson’s correlations and t -tests were conducted to assess for birth order effects.

3. Results

Figs. 1 and 2 show mean values for right and left 2D:4D ratios by diagnostic group and sex.

Univariate ANOVA for right 2D:4D was not significant for the overall model ($F=1.489$, $p=.224$), sex ($F=.855$, $p=.358$), group ($F=.151$, $p=.699$), or sex \times group interaction ($F=.2470$, $p=.120$). Univariate ANOVA for left 2D:4D was likewise not significant for the overall model ($F=.165$, $p=.920$), sex ($F=.336$, $p=.564$), group ($F=.043$, $p=.837$), or sex \times group interaction ($F=.047$, $p=.828$).

Among NCs, right 2D:4D was significantly greater in females (mean= -1.058 , S.D.=0.301) than males (mean= -1.548 , S.D.=1.256) ($t(30.552)=-1.941$,

$p=.031$), whereas left 2D:4D was not sexually differentiated (females: mean = -1.216 , S.D. = 0.635 ; males: mean = -1.328 , S.D. = 0.560 ; $t(42) = -.617$, $p = .271$). Among SPDs, there were no significant sex differences on right 2D:4D (females: mean = -1.290 , S.D. = 0.713 ; males: mean = -1.163 , S.D. = 0.359 ; $t(32) = .695$, $p = .246$) or left 2D:4D (females: mean = -1.217 , S.D. = 0.771 ; males: mean = -1.268 , S.D. = 0.495 ; $t(32) = -.236$, $p = .408$) 2D:4D.

Among males, right 2D:4D was greater among SPDs than NCs at the trend level ($t(31.095) = -1.518$, $p = .070$), whereas left 2D:4D did not differ by diagnostic group ($t(47) = -.392$, $p = .349$). Among females, there were no significant diagnostic group differences in right 2D:4D ($t(27) = 1.206$, $p = .119$) or left 2D:4D ($t(27) = .006$, $p = .498$).

One NC male from the sample was an outlier (≥ 4.0 S.D. above mean) on right 2D:4D. Therefore, analyses were repeated excluding this individual. Results held except there was no longer a trend for diagnostic group differences in right 2D:4D among males. Findings held when covarying for age and race/ethnicity.

Evidence suggests an individual's birth order correlates with right 2D:4D in men (Williams et al., 2000). Analyses revealed the absence of a significant relationship between birth order and right 2D:4D among NC males ($r = .043$, $p = .834$; 2-tailed) and all males (SPDs and NCs combined; $r = -.012$, $p = .939$). There were no significant diagnostic group differences in birth order among males ($t(44) = 1.536$, $p = .132$; 2-tailed). Thus, subsequent analyses did not covary for birth order.

Recent evidence suggests ethnic differences in 2D:4D, with 2D:4D usually larger in White/Caucasians than other racial/ethnic groups (Manning et al., 2002); this may obscure diagnostic group differences. Therefore, one-tailed t -tests were conducted separately among White/Caucasians and African-Americans, the two largest racial/ethnic groups in the sample. Among White/Caucasian males, right 2D:4D was significantly

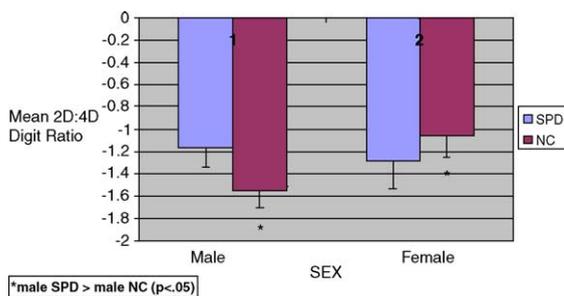


Fig. 1. Right mean 2D:4D finger digit ratios by diagnostic group and sex.

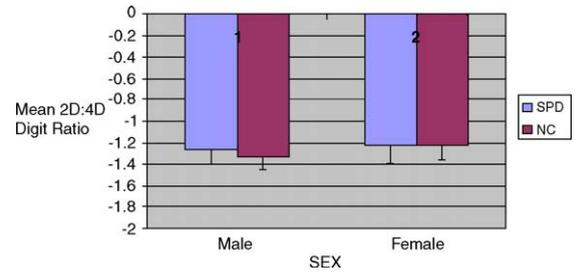


Fig. 2. Left mean 2D:4D finger digit ratios by diagnostic group and sex.

smaller in NCs (mean = -1.440 , S.D. = $.764$) than SPDs (mean = -1.081 , S.D. = 0.311 ; $t(20) = -1.753$, $p = .048$). Among African-American males, left 2D:4D was smaller among SPDs (mean = -1.580 , S.D. = 0.563) than NCs (mean = -1.162 , S.D. = 0.4265) at the trend level ($t(11) = 1.485$, $p = 0.083$); there was no significant diagnostic group difference in right 2D:4D. Among White/Caucasian females, left 2D:4D was smaller among NCs (mean = -1.440 , S.D. = 0.7718) than SPDs (mean = 0.941 , S.D. = 0.198) at the trend level ($t(8.041) = -1.763$, $p = .058$); there was no significant diagnostic group difference in right 2D:4D. Results held when including the outlier.

4. Discussion

As hypothesized and consistent with existing literature (Arato et al., 2004), among NCs, 2D:4D was more masculinized for males than females. We also replicated laterality effects, in that sex differences were only significant for the right side. Contrary to prediction, there were no significant sex differences among SPDs. However, among White/Caucasian males right 2D:4D was significantly smaller in NCs than SPDs, suggesting a more 'feminized' (or less 'androgenized') pattern in male SPDs.

Findings are consistent with several lines of evidence, which together suggest a differential sex effect whereby the male fetus may be more vulnerable to prenatal gonadal hormone disruptions than the female fetus, with subsequent sexual dimorphisms in behavioral sequelae and risk for psychopathology. First, some studies suggest that males are more vulnerable than females to adverse pre- and peri-natal events (Hultman et al., 1999). Second, evidence suggests greater vulnerability for neonatal mortality among males than females, and that sex differences in prenatal development (namely, slower lung maturation among male fetuses) likely accounts for this (Khoury et al., 1985). Third, males are generally more likely than females to

have neurodevelopmental abnormalities, which may also implicate greater cognitive and behavioral problems in males (Hoff and Kremen, 2002). Fourth, adverse pre- and peri-natal events such as hypoxia may contribute to schizophrenia (Dalman et al., 2001; O'Callaghan et al., 1992; Rosso et al., 2000), and this risk may be differentiated by sex (see Goldstein and Walder, 2006). For example, rates of obstetric complications in schizophrenia are greater for males than females in some (Foerster et al., 1991; Matsumoto et al., 2001) but not all studies (for review see Goldstein and Walder, 2006). Likewise, boys born small for gestational age or exposed to pre-eclampsia or asphyxia at birth are at an increased risk for schizophrenia compared with girls (Hultman et al., 1999).

These prior behavioral findings are relevant to neuroanatomic findings in schizophrenia and sex differences. First, there are reports of structural brain abnormalities in schizophrenia, particularly in the hippocampus, which develops during the 1st trimester. This overlaps with the period of sexual differentiation of the brain and 2D:4D (MacLusky et al., 1987). Second, evidence of hippocampal abnormalities in schizophrenia supports a link between schizophrenia and high 2D:4D given that 2D:4D has been shown to correlate with hippocampal structure in women (Kallai et al., 2005). Third, there is evidence of abnormal sexual brain dimorphisms in schizophrenia, suggesting the possibility that factors yielding normal sexual dimorphisms may have differential sex effects in their modulation of the impact of early brain insults (Goldstein et al., 2002), and may reflect prenatal gonadal hormone disruptions.

Consistent with some (not all) previous findings in schizophrenia (Arato et al., 2004), our results suggest male schizophrenia risk may relate to Alias' (1972) concept of "androgen dysgenesis" (relatively greater prenatal estrogen exposure), versus greater prenatal testosterone exposure in autism (Manning et al., 2001). This fits with Geschwind and Galaburda's (1985) brain laterality hypothesis and evidence of disrupted sex differences in language-related brain structure/function (Goldstein et al., 2002; Shaywitz et al., 1995) and cognition (Walder et al., 2006) in schizophrenia. Finally, the present findings of atypical 2D:4D ratios in males with SPD, but not females, are also consistent with evidence that males are more susceptible to adverse prenatal events.

One limitation of the present study is the small sample size, which reduced power for detecting diagnostic group and sex differences. It is noteworthy in this regard, that SPD 2D:4Ds were in reverse

direction of widely reported sex differences, and this trend may reflect an anomalous pattern that would be detected with a larger sample. We will address this possibility in future studies using larger samples.

Several other issues should also be addressed in future research. First, studies of adrenal and gonadal hormones in at-risk youth are needed (Walker et al., 2005). Second, exploration of both genetic and prenatal environmental contributions to 2D:4D will shed light on the mechanisms involved in prenatal development of 2D:4D (Manning et al., 2001). Thirdly, evidence that increased number of older fraternal siblings is associated with greater likelihood of homosexual orientation (Blanchard, 1997) suggests sex of older siblings is associated with 2D:4D (see Williams et al., 2000). In this way, the "feminization hypothesis" in schizophrenia vulnerability may be stronger among (if not restricted to) male adolescents with older brothers. Therefore, fraternal birth order effects should be considered. Finally, use of more traditional measures of 2D:4D such as photocopies of the hand or use of vernier callipers to measure finger length directly on the hand may be more sensitive and reduce measurement error.

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