The Epigenesis of Planum Temporale Asymmetry in Twins

Variation in hemispheric asymmetry of the planum temporale (PT) has been related to verbal ability. The degree to which genetic and environmental factors mediate PT asymmetry is not known. This study examined the heritability for planar asymmetry in 12 dizygotic (DZ) and 27 monozygotic (MZ) male twin pairs who were between 6 and 16 years of age. There was weak but positive evidence for heritability of planar asymmetry. Co-twin similarity for planar asymmetry and Sylvian fissure morphology increased when excluding twins discordant for writing hand and when excluding twins exhibiting birth weight differences >20% from the analyses. Birth weight differences were also related to twin differences in total cerebral volume, but not central sulcus asymmetry. These results suggest that exogenous perinatal factors affect the epigenesis of planar asymmetry development.

Introduction

Perisylvian cortex engages in language-related information processing (Ojemann, 1985). For this reason, neuroanatomical structures within the perisylvian region have been targets for studies attempting to explain the neurobiological underpinnings of reading and language disability. Symmetry or reversed asymmetry of the planum temporale (PT) is consistently related to language impairment (Plante et al, 1997). Symmetry or reversed asymmetry of the planum temporale (PT) is consistently related to language impairment (Plante et al, 1997). The atypical planar asymmetry findings in congenital adrenal hyperplasia, in which absence of 21-hydroxylation leads to high levels of intrauterine testosterone, support this theory.

This study examined PT asymmetry concordance in 27 male MZ twins and 12 DZ twins. Planar asymmetry was predicted to exhibit significant heritability based on evidence that planar asymmetry is related to a family history of reading disability. Birth weight differences, as an index of TTTS, were also examined to determine if this perinatal risk factor was related to twin discordance in planar measures.

Materials and Methods

Participants

Twenty-seven MZ and 12 DZ twin pairs were recruited from the American Academy of Child and Adolescent Psychiatry, the Virginia Commonwealth University Twin Registry, Children and Adults with Attention Deficit Disorder and the National Organization of Mothers of Twins Clubs. Female twin pairs were excluded from this study to control for random X-inactivation that might lead to more dissimilarity among female MZ twins (Jorgensen et al, 1992). Zygosity was verified using 9–14 unlinked short tandem repeat loci, by BRT Laboratories Inc. (Baltimore, MD). MZ cases which did not yield a probability of twinship >99% were tested further for a total of 21 loci. Written assent from the child and consent from the parents were obtained for each participant. This project was approved by the National Institute of Mental Health (NIMH) and the University of Florida Institutional Review Boards.

Demographic characteristics of the twins are presented in Table 1. The age range was 6.9–16.4 years for the MZ group and 6.1–15.0 years in the DZ group. MZ children were older than DZ children by 1.7 years, but this difference was not statistically significant [t(1,74) = 1.85, P < 0.10]. Socioeconomic status (SES) was determined using the Hollingshead inventory (Hollingshead, 1975) and did not differ between the MZ (range, 20–77) and DZ (range, 20–73) groups. Quantitative handedness measures were not available for this study. Handedness was defined by writing hand. Operationally defining handedness by writing hand overestimates right-handedness and underestimates the proportion of ambidextrous participants. There were no zygosity differences for SES [t(1,57) = 0.43, n.s.] or writing hand [x^2(1,74) = 0.47, n.s.].
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Records indicating whether twins were monochorionic, a risk factor for TTTS, were not available for many twins. It has been suggested (Tan et al., 1979) that a birth weight difference >20% can be used as a proxy for TTTS. MZ twins in this study were classified as having birth weight differences >20% as an index of twin transfusion syndrome. Birth weights and gestation length were determined by parental report and corroborated with medical records when medical records were available.

**MRI Protocol and Measurement Methods**

**MRI Acquisition**

Volumetric 1.5 mm thick axial images were acquired using a GE 1.5 T Signa scanner. Scan parameters consisted of a repetition time of 24 ms, an echo time of 5 ms, flip angle of 45°, a 24 cm field of view and a 192×256 matrix. These images were acquired at the National Institutes of Health.

**Image Processing**

Brain structure data collection for this study was performed at the University of Florida Mcknight Brain Institute. The images were reformatted into 1 mm thick sagittal sections to correct for tip in the coronal, axial and sagittal planes of section. Parameter files were created that stored the distance between the anterior commissure and borders of the brain. Talairach coordinates were used to identify the same medial to lateral locations in each brain. These coordinates are reliable for sagittal positions. The Talairach system standardizes positions by relating them to a brain atlas where the horizontal plane intersects the anterior and posterior commissure. The images were not warped or altered during the reformatting process. Each image was assigned a new random number to ensure that raters were blind to the zygosity and pairing of the twins.

**Data Collection Procedures**

Surface area measurements were obtained for the PT (Leonard, 2001). The Sylvian fissure is surrounded by horizontal and vertical planes of cortical tissue. The PT is defined by the horizontal bank, which extends from Heschl’s sulcus to the origin of the vertical bank or posterior ascending ramus (PP). The PP, also called the planum parietale, rises from cortical tissue. The PT is defined by the horizontal bank, which extends from the anterior commissure and borders of the brain. Talairach coordinates were used to identify the same medial to lateral locations in each brain. These coordinates are reliable for sagittal positions. The Talairach system standardizes positions by relating them to a brain atlas where the horizontal plane intersects the anterior and posterior commissure. The images were not warped or altered during the reformatting process. Each image was assigned a new random number to ensure that raters were blind to the zygosity and pairing of the twins.

**Statistical Analyses**

Chi-square, Pearson correlations and t-tests were performed to determine if variables such as writing hand, birth order and SES might confound the interpretation of the co-twin results between zygosity groups. Pearson correlations were used to examine the co-twin anatomical relations. Results from all the exploratory demographic analyses are presented and should be viewed with caution due to the possibility for type I error.

**Results**

**Writing Hand and Sylvian Fissure Morphology**

All left-handed DZ (n = 2) and MZ (n = 6) participants were second born [χ²(1,37) = 31.8, P < 0.0001] and had co-twins who were right-handed. MZ twins discordant for handedness had a shorter gestation than MZ twins discordant for writing hand [t(1,25) = 2.24, P < 0.05].

Partial correlations, controlling for twin pair, were performed to examine the relation of the planum measures to writing hand. Table 2 shows that writing hand was related to PT asymmetry in MZ and DZ twins. This finding was due to the high prevalence of a right hemisphere type V Sylvian fissure morphology in participants with a left writing hand. Six of eight left-hand writers had a type V compared to 4 of 68 right-hand writers [controlling for twin pair: partial r(1,73) = 0.619, P < 0.001].

The Witelson and Kigar classification method was also used to determine if the left and right Sylvian fissures of one twin exhibited the opposite hemispheric morphology of the co-twin. There were no hemispheric reversals of Sylvian fissure morphology in twins discordant for writing hand. One pair of right-handed MZ twins exhibited reversals of Sylvian fissure morphology. The morphology of surrounding perisylvian cortex of one twin was not, however, a reversed mirror image of the co-twin’s morphology (Fig. 1).

MZ twins were more likely than DZ twins to be discordant for right hemisphere [χ²(1,36) = 3.79, P < 0.10] and bilateral Sylvian fissure morphology [χ²(1,36) = 4.79, P < 0.05]. There was not a significant difference between the percentage of MZ twins (19%) and DZ twins (33%) that were discordant for left hemisphere Sylvian fissure morphology [χ²(1,38) = 1.03, n.s.].

**Neuroanatomical Concordance**

Pearson correlations between co-twin anatomical measures are presented in Table 3. As expected, total cerebral volume was significantly correlated between MZ and DZ co-twins. The planar asymmetry correlation coefficient approached signifi-
cance in the MZ twins. Power analysis for the planar asymmetry relation in MZ twins indicated there was low power (PT asymmetry $\beta = 0.34$).

Demographic and Perinatal Factors Affecting Planum Concordance

MZ twin pairs discordant for writing hand exhibited significantly greater absolute differences in PT asymmetry $[t(24) = 2.08, P < 0.05]$. Figure 2 shows the planar asymmetry relation between MZ co-twins, coded by writing hand discordance. Excluding twins discordant for writing hand improved the planar asymmetry correlation between MZ co-twins $[r(20) = 0.377, \text{n.s.}]$, but not the significance value.

MZ twin pairs with birth weight differences $>20\%$ exhibited greater absolute differences in PT asymmetry $[t(25) = 2.67, P < 0.05]$. Figure 3 shows the planar asymmetry relation between MZ co-twins, coded by birth weight differences. Excluding twins with birth weight differences ($>20\%$) improved the planar asymmetry correlation between MZ co-twins $[r(21) = 0.437, P < 0.05]$. The increase in planar asymmetry relation was due to the exclusion of twins with birth weight differences ($>20\%$) that exhibited discrepant left Sylvian fissure morphology.

MZ twin pairs with birth weight differences $>20\%$ also exhibited the greatest differences in TCV $[t(25) = 2.70, P < 0.05]$. Figure 4 shows that MZ twins with the greatest differences in TCV had the greatest differences in planar asymmetry $[r(26) = 0.612, P < 0.001]$. Figure 4 also shows that this relation was due, in part, to twins with birth weight differences ($>20\%$). Discordance for central sulcus asymmetry was not explained, however, by birth weight differences $[t(25) = 0.48, \text{n.s.}]$.

Discussion

The gyral and sulcal features of monozygotic twins are surprisingly dissimilar. Monozygotic twin discordance in brain structure appears to be due, in part, to intrauterine events that could lead to divergent morphological development. Weak rela-
The uniqueness of twinning is another criticism. Events related to placentation are unique for twins and limit strict comparisons to singleton development. TTTS is an example of a developmental problem largely specific to monochorionic twins (Gaziano et al., 2000). In TTTS, the arterial vasculature of one twin is shared with the venous vasculature of the other twin. This causes one twin to transfuse the cotwin, leading to hypoxia, reduced concentrations of essential amino acids, growth retardation (Gall, 1996) and depressed IQ (Munsinger, 1977) in the donor twin and hyperperfusion of the recipient twin. TTTS could alter normal brain development for the donor or recipient twin.

The increased frequency of perinatal risk factors in monochorionic monochorionic twins has led some to suggest that heritability estimates should be based on comparisons of MZ dichorionic twins to DZ twins (Corey et al., 1979). The relation between twin birth weight difference (>20%) and differences in planar asymmetry supports this point. Valid estimates of brain structure heritability must take into account intrauterine events unique to twins and chorionic status in particular.

Alternatively, MZ twins provide a model for identifying environmental variables that influence human cortical development. For example, maternal drug use has been related to discordance for congenital structural anomalies in a pair of MZ twins (Reitnauer et al., 1997). Examining the relation between brain structure concordance and the timing of pathological events could provide evidence as to when particular neuroanatomical features are most susceptible to perinatal insults.

**Comparison to Other Imaging Twin Studies**

The heritability findings for planar asymmetry are similar to findings from other twin studies for gyral and sulcal topography. It has been estimated (Bartley et al., 1997) that 7–17% of gyral patterning was due to genetic influences in 10 MZ and nine DZ adult twin pairs. In another small study, low heritability estimates were also reported for temporal lobe regions (Tramo et al., 1998). Figure 1 illustrates these findings. Even MZ twins that exhibit the same Sylvian fissure morphology demonstrate differences in tertiary gyri and sulci.

Planar asymmetry discordance and the high frequency of left hemisphere Sylvian fissure discordance in twins exhibiting birth weight differences (>20%) suggest that Sylvian fissure morphology can be affected by perinatal events. In addition, Ajayi-Obe and coworkers found that a group of infants born prematurely exhibited less gyral and sulcal complexity than full term infants, despite their similar cerebral volumes and age corrected for prematurity (Ajayi-Obe et al., 2000). The association of perinatal events with cortical development helps to explain the low heritability estimates reported by previous small sample twin studies.

Only one other study has examined PT concordance in twins (Steinmetz et al., 1995). They did not find significant concordance for planar asymmetry in 20 monzygotic twin pairs. Steinmetz et al. did report that twins discordant for handedness exhibited large discrepancies in planar asymmetry. All but one of the left-handers in the Steinmetz et al. study exhibited symmetry or reversed planar asymmetry. In contrast, the left-handed twins in this study exhibited leftward asymmetry. These left-hand writers were all second-born and more likely to be born prematurely. Hopkins et al. have shown that chimpanzee handedness is heritable (Hopkins et al., 2001), but the degree of heritability is modified by offspring parity (developmental...
Anatomical Specificity

Birth weight differences accounted for differences in MZ twin Sylvian fissure morphology, planar asymmetry and total cerebral volume. There was not a similar explanation for discordance in central sulcus asymmetry, however. Variation in central sulcus asymmetry was also unrelated between co-twins. This replicated finding (Bonan et al., 1998) suggests there are not strong genetic effects on central sulcus asymmetry. The modulating effects of perinatal events on development may be most easily seen for genetically mediated phenotypes.

If TTTS explains the birth weight differences, then the timing of TTTS influences could provide insight into planum development. The development of TTTS is not well understood, however. The influences of TTTS may be greatest after 20 weeks gestation, when placental vascular patterns are stabilized (Sebire et al., 2001). This timing appears to coincide with the period of gestation when the Sylvian fissure is developing and planar asymmetry is first seen (Wada et al., 1975; Chi et al., 1977; Bernard et al., 1988).

Developing Asymmetry

Individuals with situs inversus (reversed asymmetry of visceral organs) have been studied to determine if the same mechanisms for visceral organ asymmetry affect cerebral asymmetry. Three cases of situs inversus exhibited reversed frontal and occipital petalia (Kennedy et al., 1999). Other evidence of anomalous laterality was not found. All four subjects were right-handed, had a left hemisphere language dominance and 2/3 had leftward planar asymmetry. Although one case of right hemisphere aphasias has been reported in a stroke patient with situs inversus (Cohen et al., 1993), most situs inversus studies do not report an increased incidence of left-handedness or anomalous language organization (Woods, 1986; Tanaka et al., 1999). These studies do not support the idea that mechanisms affecting visceral organ asymmetries are related to cortical asymmetries. Perhaps similar, but different genetic mechanisms direct the development of cerebral asymmetry than for visceral organ asymmetry (Alexander and Annett, 1996).

Although little is known about the events that produce cerebral asymmetry, considerable progress has been made in understanding the cascade of events leading to asymmetric development of visceral organs. Visceral organ asymmetry is dependent on asymmetric expression of key regulatory proteins. Activin inhibits the expression of sonic hedgehog (Shh) on the right, but not left side of the primitive streak (Levin et al., 1995). Left-sided expression of Shh leads to the expression of transforming growth factor beta (TGF-β) by Nodal, which has downstream effects on the expression of Pitx2 (Levin et al., 1995). Asymmetric expression of Pitx2 leads to asymmetric development of the heart, lungs, pituitary and pineal body (Lin et al., 1999; Liang et al., 2000). The conservation of these molecular events across frogs, chickens and mice is strong evidence that similar mechanisms could regulate human asymmetries.

Discordant asymmetry may occur in twins because of placentaion and orientation of embryos. Obliquely conjoined twins provide support for this hypothesis. In conjoined twins, the twin on the right frequently exhibits laterality deficits (Levin et al., 1996). Levin suggests the parallel orientation of the two primitive streaks allows activin on the right side of the left embryo to inhibit Shh on the left side of the right embryo. This mechanism could explain mirrored lateralization for brain function in MZ twins (Sommer et al., 1999), but only for mono-chorionic monoamniotic MZ twins who make up <1% of twins (Hill et al., 1996).

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The cascade of regulatory events guiding left and right plana development could begin around 21 weeks when the Sylvian fissure develops (Bernard et al., 1988) and taper off around 29–31 weeks when planar asymmetry is first discernible (Wada et al., 1975; Chi et al., 1977). The weak heritability estimates in this study suggest that large numbers of families would be necessary to find genetic linkage for planum development. Identification of genetic expression patterns regulating planum development may require microarray studies of post-mortem human or chimpanzee fetal brains.

A large number of factors, including nutrition, probably affect genomic to synaptic levels of planum development. For example, vitamin A deficient quail embryos exhibit cardiac situs inversus. Administration of retinoic acid rescues the expression of nodal and Pitx2, and produces normal cardiac development (Zile et al., 2000). Teratogens might also affect planar asymmetry. Prenatal alcohol exposure produces neuronal migration errors in rat cortex (Hirai et al., 1999) and has been related to changes in white and grey matter in the left hemisphere temporal-parietal region of children (Sowell et al., 2001).

Summary

This study supports suggestions that PT development is mediated by genetic and experiential factors (Habib and Galaburda, 1986). Monozygotic twins exhibit weak concordance for planar asymmetry, due in part to modulating factors related to birth weight differences and writing hand discordance. These findings suggest that intraterine events can alter the direction of brain development between twins and highlight the importance of having large twin pair samples when estimating neuro-anatomical heritability. On the other hand, MZ twins may be a good model for identifying specific perinatal events and the timing of those events that negatively affect brain development and function.

Notes

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