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Original Article

Nongenetic Factors Associated with Human Handedness and Footedness in Japanese Twin Children

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Abstract

Objective: The aim of this study is to clarify the factors related to the handedness and footedness of twins using two of the largest databases on Japanese twins available.

Methods: The first group consisted of 1,131 twin pairs, all school children either 11 or 12 years old (S group), and the second group consisted of 951 twin pairs of different ages (1–15 years) in several maternal associations (M group). All data were gathered using a questionnaire. Factors associated with the handedness or footedness of twin individuals were analyzed by univariate and multivariate logistic analyses.

Results: Multivariate logistic analysis showed that for handedness, birth year (OR=1.02) and neonatal asphyxia (OR=1.62) were selected in the S group, and sex (OR=1.34), the age of twins (OR=1.56), parity (OR=1.31), gestational age (OR=1.58), and family history (OR=1.82) were selected in the M group. For footedness, birth complications (OR=1.37) were selected in the S group, and sex (OR=1.33), the age of twins (OR=1.69), gestational age (OR=1.83), and family history (OR=2.49) were selected in the M group. Factors associated with handedness and footedness specific to twins, such as zygosity, placentation, birth order within twin pairs and the sex of the cotwin, were not found, although being a twin might have some effects.

Conclusion: It was concluded that factors that affect handedness or footedness in general, such as sex, birth year, age, parity, neonatal asphyxia, gestational age, birth complications, and family history, seem to have stronger effects on handedness and footedness than being a twin.

Key words: handedness, footedness, Japanese, twin children, birth complication

Introduction

Left-handedness is a normal variant, but may result from early-life brain damage (1). There has been a long-standing debate on the complex correlation of the development of human hand preference with brain lateralization (2), and occasionally, the correlation of both hand and brain lateralizations with human mental development or diseases. Handedness, used as a proxy for cerebral lateralization (3), is a topic of considerable importance because of its potential to reveal mechanisms of the underlying pathophysiology of problems related to brain development.

The determinants of human handedness remain unknown, although numerous studies have been performed to elucidate them. The cause of hand preference in humans is a combination of behavior and genetics, but can vary from being a purely learned behavior to being based solely on genetics (4). The hypothesis that handedness is genetically determined has received mixed support (5). Recently, the author has performed, using one of the present subject groups, a genetic analysis of hand and foot preference, and found that the variances of handedness and footedness or their association is mostly attributable to nongenetic factors (6). Moreover, the results of a simultaneous analysis of handedness data from 35 twin studies revealed a small additive genetic effect accounting for 25% of the variance (7).

Of the studies that have been conducted, twin studies provide a unique opportunity for the discussion of the origin of human handedness for the following reasons. First, twin studies have often been used to analyze the genetic background of handedness by comparing the similarities between monozygotic (MZ) and dizygotic (DZ) twin pairs (6, 7). Second, the effects of complications at birth on handedness were examined, as

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twin birth itself is accompanied by many birth stressors or birth complications. Third, the so-called testosterone hypothesis (8), in which prenatal exposure to testosterone is proposed to promote the development of the right hemisphere and increase the incidence of sinistrality, can be tested by comparing the hand preferences of opposite-sex and same-sex DZ twins.

However, several problems have been pointed out regarding the use of twin data. The main issues are whether the prevalences of left-handedness between 1) singletons and twins, 2) MZ and DZ twins, 3) monochorionic (MC)-MZ and dichorionic (DC)-MZ twins, and 4) first-born and second-born twins are equal. The effect of chorion type of MZ on laterality, which depends on the timing of twinning, and is known as mirror imaging, for example, in which MC-MZ twins show a higher prevalence of left-handedness than DC-MZ twins or in which MC-MZ pairs show a higher discordant rate of handedness than DC-MZ pairs. This phenomenon has not been scientifically ascertained. Many studies have been performed using twin subjects to solve these problems; however, the results are inconsistent partly because of the small sample size used.

Following this background and the previous results obtained by this author (6), the aim of this study is to clarify mainly the nongenetic factors related to the handedness and footedness of twin individuals using the largest databases available on Japanese twins. Although the study of footedness is limited thus far, this trait may be a more sensitive indicator of lateral dominance, as it is less strongly affected by social factors than handedness.

Materials and Methods

Outline of present samples

The present samples used for analysis consisted of volunteer-based Japanese twin databases, involving two independent groups of subjects. The first group of subjects consisted of 1,131 mothers and their twin children living in the Tokyo metropolitan area. All the twins in this group had applied to the secondary school attached to the Faculty of Education of the University of Tokyo between 1981 and 2004 (school applicant group). At the time of data collection, all the twins were either 11 or 12 years old (sixth grade of primary school in Japan). Their birth years ranged from 1968 to 1992. Therefore, the secular trends of handedness and footedness of people in nearly the same age group could be analyzed.

The second group of subjects consisted of 951 mothers and their twin children in several associations for the parents of multiples throughout Japan (maternal association group). The age of the twins during data collection ranged from 1 to 15 years (mean 5.9, SD 3.8). The effects of age on handedness and footedness were analyzed using this dataset, although age almost completely negatively correlates with birth year.

None of the subjects in either group were severely retarded from the medical viewpoint with regards to physical growth and motor and language development at the time of data collection. The characteristics of both databases have been reported in detail elsewhere (9). The zygosity of the twins was determined primarily using a standard questionnaire (10), which was completed by the mothers. For the school applicant group, zygosity was also diagnosed using various DNA/genetic markers for those twin pairs who were actually admitted to the school, and this zygosity was obtained prior to that obtained using the questionnaire (9).

Data collection

Data were collected through mailed or hand-delivered questionnaires, which had nearly the same format in the two groups. The questions concerned family structure, obstetric findings on the mothers; the twins' physical growth, motor, language and mental developments, the twins' and parents' medical histories and habitual behaviors; and any behavioral problems the twins had had. Detailed obstetrical records on the mothers were obtained from the "Maternal and Child Health Handbook". In the school applicant group, one parent of each twin, usually the mother, participated in a medical interview conducted by two or three interviewers, in which their responses to the questionnaire were carefully checked.

These questionnaire surveys are now in progress. The response rates of the questionnaire were 100% for the school applicant group and approximately 70% for the maternal association group.

Handedness was assessed using the question, "Which hand would your twin children predominantly use, if possible, to write a letter?" Footedness was assessed using the question, "Which foot would your twin children predominantly use, if possible, to kick a ball?" Mothers identified the direction of handedness or footedness from three categories: "right," "either," or "left". Concerning handedness, the following question, "Have you attempted to have your twin child change the hand he/she mainly use?," was also asked. The mothers chose from two categories, "yes" or "no". This question was associated with the permanent change rather than the temporary change of hand preference. Most twin studies published thus far did not include the problem of the compulsive changing of hand preference. If the mothers answered "yes" and "from left to right," their children were treated as left-handers. In the following statistical analysis, "either" was treated as "left" in accordance with many other twin studies (e.g., 5, 11, 12).

Information on parental handedness and footedness was obtained from the maternal association groups in this study. As these questions were used to collect data on the total growth and development of twins, not specifically for the study of laterality, strict criteria or detailed questionnaires regarding the definitions of handedness and footedness were not used.

Placentation

According to Medland et al. (5), placentation can be used as a useful indicator of chorionicity. In this study, placentation was assessed by asking, "How many placentas were there at birth?", which is nearly the same question used by Medland et al. (5). Mothers identified the number of placentas from three categories: "one", "two", or "don't know". Placentation was treated as a nominal variable with two levels: MC and DC. The proportions of MZ twins who were reported to be MC were 74.4% (343/461) for the school applicant group and 74.6% (223/299) for the maternal association group, which was calculated using twin pairs with both zygosity and placentation

data. Although no objective placentation diagnoses were performed to validate the retrospectively reported placentation, the percentage was nearly 75% for both groups and similar to that reported in the literature (5, 13, 14).

Statistical methods

It is important to treat twins as pairs in genetic analysis by comparing the similarities between MZ and DZ twin pairs, whereas this restriction is not necessarily needed when dealing with general epidemiologic risk factors. The present study deals with twins mainly as individuals.

The prevalences of handedness and footedness were calculated on the basis of sex. Sex difference was tested using the χ^2 test. Next, the univariate association between mainly perinatal factors and handedness/footedness was measured using unadjusted odds ratios and 95% confidence intervals. The variables considered were the age of twins, family history, maternal age at twin birth, treatment of infertility, parity, history of previous abortion, birth weight, gestational age, nonvertex presentation, Caesarean section, birth complications, neonatal asphyxia, birth order within twin pairs, zygosity, and placentation. The birth complications included, for example, placenta previa, placental abruption, umbilical cord coiling, and twin-to-twin transfusion syndrome. The composite complication was too rare for use in individual analysis. These variables were dichotomized to reflect the presence or absence of a significant biological factor to the children. The birth weight and gestational age of the twins were generally smaller and shorter than those of singletons (15). Therefore, these variables were dichotomized by considering the standards for Japanese twins (16), and preliminary analyses were conducted to clarify the effects of these variables. On the basis of the results of univariate analyses, the association between perinatal factors and lateral preference was further examined by stepwise multiple logistic regression analysis, with a threshold significance level of 0.05. The sex, birth year and age of twins at the time of data collection were also examined, as these variables were potential confounding factors.

Finally, the special conditions related to twins were analyzed. The prevalences of left-handedness/footedness in MC-MZ and DC-MZ twins were compared to test the existence of the so-called mirror imaging in MZ twin pairs, in which MC-MZ twins were expected to show a higher prevalence of left-handedness than DC-MZ twins. Moreover, the prevalences of handedness/footedness in same-sex and opposite-sex DZ twins were compared to test the testosterone hypothesis. Twins were treated as individuals in these analyses. These comparisons were performed using the χ^2 test.

All statistical analyses were performed using SAS for Windows ver 8.12 (17).

Ethical issues

As to school applicant group, the statistical analysis of the data was clearly written in the application document, and the detailed explanations concerning data collection by questionnaire and interview, and blood sampling for zygosity examination and health check were added as another paper from 1999 on. Moreover, informed consent was obtained from each twin and his or her parents in writing from 2001 on as part of the application process. The data analysis was also permitted by the twin research committee of this school. When present study was performed, this school did not have ethical committee of twin study, which has been now under construction, including the author as one of the advisers. Zygosity diagnosis using DNA sample was permitted through ethical committee of Graduate School of Medicine, the University of Tokyo.

All the mothers in the maternal association group cooperated voluntarily in this research, mainly through their associations.

Results

The numbers of twin individuals or pairs in the frequency categories for handedness and footedness are given in Table 1. The prevalences of left-handedness were 14% in males and 13% in females in the school applicant group, and 26% in males and 22% in females in the maternal association group. The prevalences of left-footedness were 12% in males and 10% in females in the school applicant group, and 17% in males and 13% in females in the maternal association group. As for the sex difference, both left-handedness and left-footedness were more common in males than in females, although not necessarily to a statistically significant degree. As for the group difference, both left-handedness and left-footedness were more common in the maternal association group than in the school applicant group with the significant level $p<0.01$, irrespective of sex.

The prevalences of left-handedness and left-footedness in the maternal association group according to four age classes, that is, 1–3, 4–6, 7–9, and 10–15, were 32.6% (191/585), 23.4% (126/539), 20.1% (74/368), and 20.2% (71/352) for left-handedness, and 23.9% (105/439), 18.6% (88/472), 13.5% (43/319), and 14.1% (44/313) for left-footedness, respectively. These prevalences decreased until 7–9 and then stabilized after 7–9. In the following analysis, the age of twins was dichotomized, into 1–6 or 7–15, by considering this result.

Table 2 shows the results of the univariate association between perinatal factors and the laterality of the hand and foot. Left hand preference was significantly associated with an older maternal age in the school applicant group and with younger twins, a positive family history, primiparity, a birth weight below 2000 g, and a shorter gestational age in the maternal association group. Left foot preference was significantly associated with birth complications in the school applicant group and with a young age of twins, a positive family history, and a shorter gestational age in the maternal association group. The effects of birth order within twin pairs, zygosity, and placentation were not observed for either handedness or footedness irrespective of the subject group.

Table 3 shows the results of multiple logistic regression analyses. For handedness in the school applicant group, birth year and neonatal asphyxia were selected. The effect of birth year was weak. Neonatal asphyxia showed an odds ratio of 1.62. For handedness in the maternal association group, the sex, age, parity, gestational age, and family history of twins were selected. Birth weight was not selected, whereas gestational

Table 1 Prevalences of handedness and footedness measured on the basis of sex

Twin individuals	School applicant group					Maternal association group				
	Males[a] (N=1057)		Females[a] (N=1205)		p-value[b]	Males[a] (N=982)		Females[a] (N=920)		p-value[b]
Handedness										
R	854	80.8%	1007	83.6%	0.292	691	70.4%	691	75.1%	0.024*
L	147	13.9%	152	12.6%		259	26.4%	203	22.1%	
p-value[c]	<0.0001**		<0.0001**							
U	56	5.3%	46	3.8%		32	3.3%	26	2.8%	
Footedness										
R	821	77.7%	966	80.2%	0.095	645	65.7%	618	67.2%	0.030*
L	125	11.8%	117	9.7%		163	16.6%	117	12.7%	
p-value[c]	<0.0001**		<0.0014**							
U	111	10.5%	122	10.1%		174	17.7%	185	20.1%	

Twin pairs	Same-sex				Opposite-sex (N=127)		Same-sex				Opposite-sex (N=208)	
	MM (N=465)		FF (N=539)				MM (N=387)		FF (N=356)			
Handedness												
RR	325	69.9%	393	72.9%	96	75.6%	198	51.2%	219	61.5%	110	52.9%
RL/LR	103	22.2%	103	19.1%	27	21.3%	146	37.7%	101	28.4%	76	36.5%
LL	10	2.2%	21	3.9%	2	1.6%	28	7.2%	25	7.0%	16	7.7%
RU/UR	0	0%	0	0%	0	0%	2	0.5%	1	0.3%	2	1.0%
LU/UL	0	0%	0	0%	0	0%	1	0.3%	0	0%	0	0%
UU	27	5.8%	22	4.1%	2	1.6%	12	3.1%	10	2.8%	4	1.9%
Footedness												
RR	319	68.6%	395	73.3%	94	74.0%	208	53.8%	211	59.3%	118	56.7%
RL/LR	84	18.1%	68	12.6%	17	13.4%	70	18.1%	51	14.3%	43	20.7%
LL	12	2.6%	21	3.9%	2	1.6%	29	7.5%	14	3.9%	12	5.8%
RU/UR	0	0%	2	0.4%	0	0%	13	3.4%	8	2.3%	4	1.9%
LU/UL	2	0.4%	0	0%	1	0.8%	4	1.0%	0	0%	2	1.0%
UU	48	10.3%	53	9.8%	13	10.2%	63	16.3%	72	20.2%	29	13.9%

The children who use either hand or who now use the right hand, but who have experienced compulsive changes in hand preference were treated as left-handed.

R: right-handedness/footedness, L: left-handedness/footedness, U: unknown, RR: right-handed/footed concordant twin pairs, RL/LR: discordant twin pairs, and LL: left-handed/footed concordant twin pairs.

RU/UR: the handedness/footedness of one twin is unknown and the other is right-handedness/footedness, LU/UL: the handedness/footedness of one twin is unknown and the other is left-handedness/footedness, UU: the handedness/footedness of both twins are unknown.

MM: male-male, FF: female-female.

[a] Numbers include both same-sex and opposite-sex twins.

[b] The sex difference in prevalence was tested using the χ^2 test, excluding twins with unknown handedness/footedness.

[c] The group difference in prevalence was tested using the χ^2 test on the basis of sex, excluding twins with unknown handedness/footedness.

* $p<0.05$, ** $p<0.01$.

age was selected. For footedness in the school applicant group, only birth complications were selected. For footedness in the maternal association group, the sex, age, gestational age, and family history of twins were selected.

The largest odds ratios of the family history were obtained for both handedness (OR=1.82) and footedness (OR=2.49). This effect was clearer for footedness than for handedness. Many males in the maternal association group were left-handed or left-footed, but this tendency was not clearly observed in the school applicant group.

Table 4 shows the prevalences of handedness and footedness measured on the basis of the placentation of the MZ twins. There were no significant differences in the prevalences between the MC-MZ and DC-MZ twins irrespective of sex.

Table 5 shows the prevalences of handedness and footedness measured on the basis of the sex of the cotwin in the DZ pairs. There were no significant differences in the prevalences irrespective of the sex of the cotwin, with one exception, that is, the left-footedness of females in the school applicant group.

Discussion

Prevalences of handedness and footedness

The prevalence of handedness or footedness depends on the age of the subjects at the time of data collection, the method of measurement, demographics and other factors. Therefore, the prevalence varies in the reports, which makes it difficult to compare the results.

The prevalences of left-handedness among the present subjects were 13.9–14.7% in males and 12.6–13.1% in females (including or excluding the unknown subjects) in the school applicant group, as shown in Table 1. In the present study, the author treated the children who use either hand or who now use the right hand, but who have experienced compulsive changes

Table 2 Associations of mainly perinatal factors with left-handedness and left-footedness and unadjusted odds ratios (ORs) and 95 percent confidence intervals (CIs) for each item

	Left-handedness				Left-footedness			
	School applicant group		Maternal association group		School applicant group		Maternal association group	
	N	%	N	%	N	%	N	%
Age of twins								
<7 years	—		317	28.2	—		193	21.2
≥7 years	—		145	20.1	—		87	13.8
OR (95% CI)	—		**1.56**	**1.25–1.95**	—		**1.68**	**1.23–2.22**
Family history								
Yes (one or both parents)	—		135	34.3	—		68	31.5
No (no parent)	—		314	22.5	—		197	15.8
OR (95% CI)	—		**1.79**	**1.41–2.29**	—		**2.45**	**1.77–3.39**
Maternal age at twin birth								
≥30 years	137	15.6	276	26.0	96	11.6	168	19.7
<30 years	160	12.5	186	23.8	144	12.0	112	16.3
OR (95% CI)	**1.29**	**1.01–1.65**	1.12	0.91–1.39	0.96	0.73–1.27	1.26	0.97–1.64
Infertility treatment								
Yes	6	9.7	153	27.5	6	10.0	97	21.0
No	266	13.8	301	24.1	217	12.1	180	17.1
OR (95% CI)	0.67	0.29–1.57	1.20	0.95–1.50	0.81	0.35–1.91	1.29	0.98–1.70
Parity								
Primipara	143	12.6	339	26.6	122	11.4	203	18.7
Multipara	156	15.3	123	21.6	119	12.4	77	16.7
OR (95% CI)	0.80	0.63–1.02	**1.31**	**1.04–1.66**	0.91	0.70–1.19	1.15	0.86–1.53
History of previous abortion								
Yes	77	15.8	96	24.2	51	11.2	68	21.3
No	194	13.0	366	25.3	171	12.2	212	17.4
OR (95% CI)	1.25	0.94–1.67	0.94	0.73–1.22	0.91	0.66–1.27	1.28	0.95–1.74
Birth weight								
<2000 g	45	15.3	114	30.4	40	14.1	63	20.3
≥2000 g	253	13.6	344	23.6	201	11.6	213	17.4
OR (95% CI)	1.14	0.81–1.61	**1.42**	**1.10–1.82**	1.25	0.87–1.80	1.21	0.88–1.65
Gestational age								
<35 weeks	28	15.4	80	32.9	22	12.7	52	26.4
≥35 weeks	267	13.9	373	23.8	213	11.9	223	16.9
OR (95% CI)	1.13	0.74–1.72	**1.57**	**1.17–2.10**	1.08	0.68–1.73	**1.76**	**1.25–2.50**
Non-vertex presentation								
Yes	68	13.7	122	27.4	57	12.3	72	19.5
No	188	13.5	299	24.3	155	11.7	183	17.8
OR (95% CI)	1.02	0.76–1.37	1.18	0.92–1.50	1.06	0.77–1.47	1.12	0.82–1.51
Caesarean section								
Yes	59	13.9	244	26.6	52	13.0	149	19.2
No	238	13.8	216	23.5	188	11.6	129	16.9
OR (95% CI)	1.00	0.74–1.36	1.18	0.96–1.46	1.13	0.82–1.57	1.16	0.90–1.51
Birth complications								
Yes	177	14.7	287	25.3	151	13.4	170	17.9
No	122	12.7	88	25.2	91	10.1	52	16.9
OR (95% CI)	1.19	0.93–1.52	1.00	0.76–1.32	**1.37**	**1.04–1.81**	1.08	0.77–1.51
Neonatal asphyxia								
Yes	23	19.7	34	27.2	18	16.4	20	20.4
No	269	13.5	411	25.0	218	11.6	252	18.1
OR (95% CI)	1.57	0.98–2.52	1.12	0.75–1.69	1.49	0.88–2.53	1.16	0.70–1.93
Birth order								
Second-born	152	14.1	247	26.9	108	10.7	143	18.5
First-born	147	13.6	215	23.3	134	13.2	137	17.8
OR (95% CI)	1.04	0.81–1.33	1.21	0.98–1.50	0.79	0.60–1.03	1.05	0.81–1.36
Zygosity								
Monozygotic	201	13.9	221	25.3	158	11.5	136	18.6
Dizygotic	75	13.9	196	24.6	63	12.6	121	18.0
OR (95% CI)	0.99	0.75–1.32	1.04	0.83–1.30	0.91	0.66–1.24	1.05	0.80–1.37
Placentation								
Monochorion	109	13.8	131	25.1	87	11.7	78	17.8
Dichorion	80	16.3	198	25.5	58	12.5	121	18.6
OR (95% CI)	0.83	0.60–1.13	0.98	0.76–1.27	0.93	0.65–1.32	0.95	0.69–1.30

OR indicates the risk of left-handedness given a particular condition. In each case, the category of the numerator is listed first. The comparison group is right-handedness.

95% CIs significantly greater than 1.0 are shown in bold font.

Table 3 Results of multiple logistic analysis regarding factors associated with left-handedness and left-footedness

	Left-handedness		Left-footedness	
	Adjusted OR	95%CI	Adjusted OR	95%CI
School applicant group (N=2102)				
Sex	not selected		not selected	
Birth year (1968–1992)	**1.02**	**1.00–1.04**	not selected	
Maternal age	not selected		—	
Neonatal asphyxia	**1.62**	**1.01–2.60**	—	
Birth complications	—		**1.37**	**1.04–1.81**
Maternal association group (N=1748)				
Sex	**1.34**	**1.08–1.68**	**1.33**	**1.00–1.75**
Age of twins	**1.56**	**1.24–1.98**	**1.69**	**1.26–2.27**
Parity	**1.31**	**1.03–1.67**	—	
Birth weight (g)	not selected		—	
Gestational age (weeks)	**1.58**	**1.17–2.13**	**1.83**	**1.28–2.62**
Family history	**1.82**	**1.42–2.33**	**2.49**	**1.79–3.46**

The categorization of the variables is shown in Table 2. Birth year was treated as a continuous variable.
95% CIs significantly greater than 1.0 are shown in bold font.

Table 4 Handedness and footedness according to placentation of MZ twins

	Handedness						Footedness					
	School applicant group			Maternal association group			School applicant group			Maternal association group		
	Right	Left	p-value	Right	Left	p-value	Right	Left	p-value	Right	Left	p-value
Male twins												
Monochorionic	260	44		176	67		246	38		171	45	
Dichorionic	91	15	0.935	62	24	0.952	91	9	0.250	59	18	0.641
Female twins												
Monochorionic	306	52		153	41		308	38		138	17	
Dichorionic	104	20	0.666	44	20	0.099	108	14	0.882	43	6	0.805

Twins were treated as individuals.
Differences were tested using the χ^2 test.

Table 5 Handedness and footedness between opposite-sex and same-sex dizygotic twins for males and females

	Handedness						Footedness					
	School applicant group			Maternal association group			School applicant group			Maternal association group		
	Right	Left	p-value	Right	Left	p-value	Right	Left	p-value	Right	Left	p-value
Male twins												
Same-sex	122	28		133	49		122	22		125	25	
Opposite-sex	101	24	0.911	147	56	0.884	99	15	0.630	146	31	0.839
Female twins												
Same-sex	122	16		170	39		111	19		145	27	
Opposite-sex	118	7	0.086	151	52	0.089	106	7	0.034*	137	38	0.151

This table shows the prevalences of handedness and footedness measured on the basis of the sex of the cotwin in dizygotic pairs. Twins were treated as individuals.
Differences were tested using the χ^2 test.
* $p<0.05$.

in hand preference as left-handed. These prevalences are higher than those expected in singletons. According to Hatta and Kawakami (18), the prevalences of non-right-handers among male and female Japanese students (mainly college students) were 13% and 8% in 1993, respectively, and the prevalences of left-handers have been gradually increasing. Cultural pressure to use the right hand has not been very strict recently in Japan, particularly in urban areas. The high prevalence of left-handedness in the school applicant group may be partly related to the fact that the subjects all live in the center of Tokyo, where the degree of cultural pressure to use the right hand may be relatively low.

The results of the large-scale twin studies that have been published to date are summarized in Table 6. Compared with those of other studies, the prevalence of left-handedness ('left' and 'either') in the school applicant group was not high. Using

Table 6 Summaries of twin studies on handedness using large sample size of more than 700 pairs

	Total number of pairs	Age	Handedness criteria	Observed frequencies (pairs)[a]			Left handedness[a] (%)		
				RR	RL/LR	LL	Prevalence[b]	RL/LR pairs[b]	LL pairs[b]
Loehlin & Nichols (1976)[c]	Unknown	Adults	Self-classification	641	193	13	12.9%	22.8%	1.5%
Neale (1988)	1687	8–80 years	Self-classification	1281	341	46	13.0%	20.4%	2.8%
Orlebeke et al. (1996)	1663	12–22 years	Self-classification	1239	377	47	14.2%	22.7%	2.8%
Derom et al. (1996)	760	6–28 years	Self-classification	525	195	40	18.1%	25.7%	5.3%
Ross et al. (1999)[c]	Unknown	Unknown	Hand performance for 5 tasks	1728	369	34	10.3%	17.3%	1.6%
Basso et al. (2000)[c]	Unknown	Unknown	Self-classification	2811	383	35	7.0%	11.9%	1.1%
Medland et al. (2003)	7419	Wide range[d]	Throwing hand	3944	1166	169	14.2%	22.1%	3.2%
Medland et al. (2006)	35 studies included	Unknown	Depending on research	16378	4193	556	12.6%	19.8%	2.6%
Present study									
School applicant group	1131	11–12 years	Maternal report	814	233	33	13.8%	21.6%	3.1%
Maternal association group	951	1–15 years	Maternal report	527	323	69	25.1%	35.1%	7.5%

[a] Ambidextrous subjects are considered left-handers. The author calculated these values using the data reported by Medland et al. (7). The calculation was performed using pairs with both twins' complete data on frequency. Sex differences were not considered.
R: right-handedness and L: left-handedness.
[b] Prevalence (%): % of left-handed twins, RL/LR pairs (%): % of discordant twin pairs, and LL pairs (%): % of left-handed concordant twin pairs.
[c] Cited from Medland et al. (7).
[d] Age was defined as years from birth rather than age at the time of data collection.

35 samples of the twin studies to date (with a combined sample size of 21,127 twin pairs) reported by Medland et al. (7), the author calculated the prevalence of left-handedness in twin individuals to be 12.6% (5,305/42,254). The prevalence obtained in the present study in the school applicant group was not significantly different from that obtained by Medland et al. Moreover, when both sets of data (school applicant and maternal association groups) were compared for subjects in the same age group, that is, the 11 and 12 year olds, the prevalences of left-handedness and left-footedness were not statistically different between the two groups, that is, 14% (299/2160) vs 19% (25/134) for left-handedness and 12% (242/2029) vs 12% (14/115) for left-footedness.

Regarding whether the prevalence of left-handedness between singletons and twins differs, several studies with large sample sizes have been performed. Of these studies, those of Orlebeke et al. (12) and Medland et al. (5) showed that the prevalence of left-handedness in twins is not higher, whereas those of Boklage (19), Coren (20), Davis and Annett (21), Derom et al. (13) and Sicotte et al. (22) showed a high prevalence of left-handedness in twins. In the study of Davis and Annett (21) for a large adult population (N=33,401), twins were more likely to be left-handed irrespective of age group and sex. As the control data of singletons was not available in the present study, the prevalence could not directly be compared between twins and singletons.

There have only been very limited number of studies on twin-footedness. Of these studies, that of Reiss et al. (23) showed no difference in the prevalence of left-footedness of twins compared with that of singletons. It also showed no difference in prevalence between MZ and DZ twins, although the sample size was 100 pairs. However, Williams et al. (24) observed a higher prevalence of left-footedness in twins than in control singletons (OR=2.0).

Secular trend and age effect on handedness

The secular trend of handedness, mainly explained by cultural pressure, is well documented in singletons. At the time of data collection the age of all the school applicants was 11 or 12 years, and their birth years ranged from 1968 to 1992. The results shown in Table 3 may reflect a slight secular trend of handedness. If birth years are divided into two groups, that is, 1968–1980 and 1981–1992, the prevalence increases slightly from 13% (162/1280) to 16% (137/880). Neale (11) observed a slight increase in the proportion of right-handers in twins with age (range 8–80 years). He regarded this phenomenon as more likely to be associated with a secular trend, namely reduced cultural pressure to become right-handed, than with left-handers becoming right-handers as they age. It is difficult to show a stable secular trend because the present sample size was still small.

The age of the twins clearly affected on handedness in the maternal association group, as shown in Table 3. Since the age of the twins in the maternal association group almost completely negatively correlates with birth year, the results shown in Table 3 alone do not indicate the age effect on handedness. However, as shown in the Results section, the prevalence decreased rapidly with age from 33% (1–3) to 20% (7–9). This rapid decrease did not seem to be explained by a secular trend or cultural pressure. According to Janβen (25), handedness changes frequently during normal development and seems to stabilize only at the ages of 3 to 4 years. The higher prevalence of the maternal association group than the school applicant group seems to reflect the difference in age distribution between the two groups. One possible explanation is that many young twins in the maternal association group are 'ambidextrous', who were defined as left-handed according to many other twin studies. The prevalence of ambidextrous subjects in the maternal association group decreased from 8% (90/1124)

in 1–6 years to 2% (13/720) in 7–15 years. Perhaps many ambidextrous subjects become right-handed as they grow older, although a direct estimation requires longitudinal data.

Factors associated with handedness/footedness

Several birth stressors, such as neonatal asphyxia, birth complications, and a short gestational age were associated with left-handedness/footedness, although specific determinants were not detected. According to Williams et al. (24), both infant resuscitation and the birth stress significantly affected the handedness and footedness of 5-year-old children. The present study also supports this finding.

The effects of zygosity, chorionicity/placentation, birth order within twin pairs, and sex combination on sidedness are problems unique in twins. Many studies of such problems have been performed, and controversial results have been obtained. Of these results, those obtained using large sample sizes were as follows. Regarding the difference in prevalence of zygosity, Sicotte et al. (22) and Medland et al. (5) did not observe a difference between MZ and DZ twins, whereas Orlebeke et al. (12) observed a higher prevalence of left-handedness in MZ twins, particularly males. The present results did not show a zygosity difference in either handedness or footedness, as shown in Table 2.

Some researchers believe that the so-called mirror imaging can be observed in MZ pairs. However, negative results on this phenomenon have accumulated (5, 13, 22, 26). The present study also did not reveal the effects of placentation on either handedness or footedness in MZ twins, as shown in Table 4.

The effect of birth order within twin pairs has recently been discussed (12, 27). According to James and Orlebeke (27), the hazards associated with being first-born in twin pairs (e.g., trauma) are more closely associated with left-handedness than those associated with being second-born (e.g., hypoxia). Because the birth weight of first-born twins is generally higher than that of second-born twins, the association between low-birth-weight and left-handedness in twins is weaker than that observed in singletons. Derom et al. (13) observed a slightly higher prevalence of left-handedness in first-born twins (18%) than in second-born twins (16%), although it was not statistically significant. On the other hand, Elkadi et al. (8) and Medland et al. (5) did not observe birth order effects. Moreover, Boklage (19) observed a 1.8-fold higher prevalence of left-handedness in the second-born members of same-sex discordant pairs, suggesting the secondary effect of hypoxia or acidosis. The results were thus inconsistent. The present results did not reveal any association between birth order and left-handedness, as shown in Table 2. It was also suggested that the effect of low birth weight on left-handedness is smaller than that of short gestational age, although the increased prevalence of left-handedness has often been reported in children with a very low birth weight, for example, below 1000 g (28).

The effect of the sex of the cotwin was not observed in either males or females, as shown in Table 5. Although the prevalence of the left-footedness in females in the school applicant group showed a significant association with the sex of the cotwin, the prevalence was higher in females in same-sex pairs than in females in opposite-sex pairs. This result did not support the testosterone hypothesis, as the effects of testosterone, if existing, is expected to increase the prevalence of left-handedness in females in opposite-sex pairs. This result was in accordance with that of Elkadi et al. (8). Apart from the problem of testosterone transfer from a male fetus to a female fetus in opposite-sex twins, there seems to be no difference in hand preference between opposite and same-sex DZ twins for either sex.

The effect of family history was the largest, particularly for footedness. Familial left-handedness, including families with twin children, has been well established from research performed decades ago (19, 29–31). A clear association of parental handedness with the handedness of their children was observed by evaluating 25 studies on families (32). These results from research on families are generally not controversial. However, they do not provide a conclusive explanation of the causes of left-handedness, as genetic and shared environmental factors on handedness were not separated by familial handedness. A recent study by the author (6) showed that the etiologies of handedness and footedness or their association is mostly attributable to nongenetic factors rather than genetic factors. The twin family study design is one of the best available approaches to solve this problem in more detail. According to Bishop (33), who used 150 families with twin pairs, the parent-offspring similarity of handedness was attributed to cultural transmission rather than to genetic effects. The present data allows for this type of analysis, which will be conducted in the future.

Limitations

The limitations of this study are as follows. First, it did not have control data on singletons, so a direct comparison of the prevalence between twins and singletons could not be performed. Second, the prevalence was calculated using only retrospective maternal reports, not using systematic questionnaires or observations; therefore, a certain unexpected bias may be involved. Third, the longitudinal age effect was not considered. Since behavioral characteristics in childhood vary greatly with age, it is desirable to increase the accuracy of information about the age of occurrence and duration of handedness and footedness.

Conclusion

In the present study, some of the features involved in the handedness and footedness of twins were clarified. The effects of zygosity, placentation, birth order within twin pairs, and the sex of the cotwin were not observed for either group regarding handedness or footedness. No factors associated with handedness or footedness specific to twins were identified in this study, although being a twin itself may have some effects. It was concluded that factors affecting handedness or footedness in general, such as sex, birth year, age, parity, neonatal asphyxia, gestational age, and family history, seem to have a stronger effect than being a twin.

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