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Birthweight Differences, The Transfusion Syndrome and The Cognitive Development of Monozygotic Twins

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Abstract. Monochorionic twins may differ from dichorionic monozygotic (MZ) twins because of the transfusion syndrome and the timing of the cleavage of the zygote. Intrapair birthweight differences may be an indicator of these intrauterine variables. Previous evidence concerning weight differences and intellectual ability in MZ twins is reviewed with recommendations that future research also incorporates full placental data. Poorer scores on a nonverbal test are found for the lighter male twin of pairs with large intrapair differences in birthweight. Co-twin concordance rates for test scores are also highest for this group indicating that they vary consistently from other groups. Some evidence is presented from the present and earlier studies implicating anomalies of asymmetry or the transfusion syndrome as possible causes of these differences in brain functioning. The study adds further doubts as to the validity of any assumption of developmental equivalence between MZ twins and the general population.

Key words: Birthweight, Feto-fetal transfusion, Monochorionic twins, Cognitive development

INTRODUCTION

Monozygotic (MZ) twins result from the splitting of a single egg but are not a homogeneous group. Prenatally the source of this variation relates to differences in the timing of zygote division which is reflected in the form of placentation including choronicity [33]. It is believed that dichorionic (DC) placentation results if division occurs within approximately 3-4 days and that approximately 20-30% of all MZ twins are dichorionic and the remaining two thirds monochorionic (MC) [18]. However, reported incidences of DC MZ vary from 18% to 46% [14,17,19,23,37,38,46]. Twinning is a fairly random process distributed over the first 14 days of development [8,33] and its relationship to form of placentation is more fully described by

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several authors [12,33].

In MC twins only, a blood transfer from one twin (the donor) to the other (the recipient) may occur during intrauterine life [7,8]. This vascular interconnection is almost always [2,7,14,44] or invariably [9] present in all MC twins. Based on pathological examinations of placentas, Strong and Corney report that there is some interconnection between fetal circulations in 90% of MC twins [44].

While minor degrees of anastomoses may pass unnoticed [14], in acute cases they can lead to a significant difference in blood hemoglobin levels at birth with the donor twin often anaemic and the recipient twin plethoric but equally developed. It is the one way circulation, generally artery to vein, which causes an imbalance of blood supply between the twins and can result in, depending on its severity, noticeable birthweight differences (BWD) between cotwins. The donor twin may be, in addition, smaller in weight or length or even perish to form a fetus papyraceus, while the recipient twin is larger and sometimes shows acute hydramnios [8,14].

The vascular anastomoses can only be detected by a pathologist by means of a thorough examination of the placenta after birth which includes the injection of a lightly coloured watery solution into surface vessels according to the method described by Benirschke [6]. Consequently, diagnosis of the syndrome is still somewhat arbitrary and depends on a combination of clinical, anatomical and hematological criteria [28]. A weight difference of 500 g or more [33] or a hemoglobin discrepancy of 5 g/100 ml [40] has been suggested as indicative of the presence of the syndrome, but it has been variously diagnosed as occurring in 2-3% [44], 15%, [40], 15-30% [11] or 23% [23] of live-born twins. Opinion differs as to whether the superficial artery-to-artery or vein-to-vein anastomosis, so common in normal placentas, can exist alongside the more severe vascular communication of the twin transfusion syndrome. Some [2] state that they are totally absent, but a more recent study [46] found in their series of 32 diagnosed cases of the syndrome that artery-to-vein (or vein-to-vein) circulation both coexisted with artery-to-artery or existed alone and led to a severe form of the syndrome, but most twins survived. The vein-to-vein combined with artery-to-artery anastomoses produced the worst fetal outcome with a mortality rate of 40%. A prenatal mortality rate of around 14% had been reported in earlier studies [14,2] but the Japanese study [46] found an overall survival rate of only 70%.

Despite a "plea" to the obstetrician by Benirschke [6] and others [20,44] during the 1960s, that such accurate placental data be recorded at birth, the practice is still not widespread and may be the main reason why most studies of twins either fail to recognize these potentially important differences in the prenatal environment or do not have the necessary placental data to take them into account [8,16]. Even in the 1950s Price [39] warned that interpretations of twin differences are not valid unless intrauterine variations have been considered and others since have reemphasized their warning [3,16,5]. As well as the obvious implications for genetic analysis using twins, intrauterine differences could well be critical to the long-term cognitive development of twin children.

Since the relevant placental information is still rarely obtainable retrospectively, the presence of the twin transfusion syndrome and therefore of monochorionicity can be fairly reliably deduced from large birthweight differences between cotwins, though not invariably [11,28]. However, only very few studies on longer term effects have been conducted, most studies are not recent and they present significant methodological deficiencies. The possible relationship of these weight differences to the transfusion syndrome is rarely explicitly stated and is still poorly understood by some researchers[3,4]. Even fewer studies have examined the effects of the severity of the syndrome, as indicated by magnitude of weight difference. Some early studies have in fact focused only on the performance on tests of the heavier and lighter twins without regard to the size of the weight difference [15,34,42].

Overall, research on the relationship of being the smaller (donor) or larger (recipient) cotwin of a MZ pair has been inconclusive as the following brief discussion of the most relevant studies shows.

In 1964 the performance of 16 sets of "like sex" twins from 4.5 to 11 years of age, where the lighter twin was at least 25% smaller and weighed less than 2,000 g at birth, was examined on the Stanford-Binet IQ test, the Peabody Picture Vocabulary test (PPVT) as well as on speech development and physical growth measures [3]. For the 9 MZ sets (as determined by bloodtyping and physical appearance), they found a significant difference of 6.6 Binet IQ points and 2.7 PPVT IQ points in favour of the heavier twin.

A year later, Churchill [15] tested 50 sets of twins aged between 5 and 15 years for the relationship between birthweight (BW) and performance on the Wechsler Intelligence Test for Children (WISC). While he found a lower IQ for the lighter cotwins in the whole sample when MZ and DZ twins were analysed separately, there was only a statistically significant difference in the 22 identical sets, 13 of whom were MC and the other 9 "clinically identical". However, when the WISC IQ of the MZ group was divided into the Verbal and Performance Scales, the cotwin mean difference of the Performance section was highly significant ($P < 0.0005$) but the Verbal section was not. While the finding of a lower nonverbal score for the lighter twins is interesting, this paper did not examine the relationship between weight differences and ability.

In a study of the IQ scores of 19 pairs of MZ twins, among the 8 male pairs the smaller twin scored lower in every case, while there was no difference in the 11 female pairs [20]. However, only in a quarter of the pairs did the weight difference exceed 10%. There was no difference in the DZ sample except where birthweight difference (BWD) exceeded 25%.

Kaelber and Pugh [30] presented their own data on a comparison of twins with marked BWD while reanalysing the data of earlier studies which they believed depended on numerically small and highly selected samples. They studied 374 twin sets born in four major Boston hospitals in the 1950s. The Stanford-Binet was administered to 40 sets, the remainder received group IQ tests. Although not significant, the mean score of the heavier twins was higher than the mean score of the lighter on all tests. When amount of BWD (> or < 300 g) was taken into account, the mean of the IQ difference was significant only in "like sex" pairs and favoured the heavier twin. For the 44 MZ pairs, only 5 were bloodtyped and 20 were found by a pathology examination to have a single chorion, with the remainder classified only by a physician's statement on the birth record form. The "MZ" pairs with BWD > 300 g had a mean IQ difference of 5.76 points in favour of the heavier twin but no such association was found in the 27 pairs with small BWD or in the DZ sets. A later erratum [31] reduced the IQ advantage from 5.76 to 5.13 IQ points, no longer a statistically significant difference. This was because 2 of the 17 "MZ" pairs had been misclassified and were DZ and it is still possible that the earlier finding could be statistically significant with a larger sample. Their reanalysis of Churchill's 1965 data, while it found a significant difference between birthweight and IQ in the 17 "like sex" pairs with a 300 g cotwin BWD, was not useful because zygosity was not accurately determined even though Churchill's original data provided it. Kamin [30] reanalysed this data more validly using 22 MZ twins and found no significant difference between the heavier twins from the smaller and larger (or 300 g) BWD groups.

A more recent study [4] retested the 9 MZ pairs from an earlier sample who, as well as being tested at a mean age of 8 years, were tested at a mean age of 13 years on the WISC Verbal

Scale and the PPVT. The difference of 8.7 and 7.4 IQ points, respectively, in favour of the heavier twin was significant on both measures and increased over the five-year period. Eight of the pairs who had reached a mean age of 18 years were again compared, but only on high-school records and aptitude test, and while the superiority of the larger twin persisted, it is not clear what the tests are measuring. Only in school achievement did some equalization occur and the authors suggest that the smaller twin may have attempted to compensate.

In 1974, Fujikura and Froelich [24] also reviewed the earlier studies and questioned the fairly consistent finding of IQ differences between MZ cotwins of different BW because of their small sample sizes, retrospective data and dubious methods of establishing zygosity and drawing particular attention to Kaebler and Pugh's subsequent erratum [31]. They undertook a prospective study of 125 MZ sets with unequal cotwin BW. To minimize the effect of variation in BW, the percentage difference in BW (PBD) was calculated as follows: 100(A - B)/A, where A was the BW of the heavier twin and B that of the lighter. Both black and white twins were included, but only the findings for the white group are discussed here.

The small weight difference group of $< 15\%$ PDB ($N = 16$) was compared with the large weight difference group $> 15\%$ PDB ($N = 11$) on the Bayley Mental and Motor Scale at 8 months and the Stanford-Binet at 4 years, and there were no significant differences in the IQ of cotwins in either the small or large PDB group. However, although not significant, the difference was 4.73 Stanford-Binet IQ points in favour of the heavier twins in the large PDB group.

Since this refutation of earlier findings claiming a higher IQ for the heavier twin, particularly in pairs with large BWD, there seems to have been little further research carried out on the question of BWD and intellectual development. This is regretable considering the limited age range of the children in the sample, the small number of sets in the large PDB groups of which only three are male, and the obvious bias of the investigators who stated, "It is our opinion that contrary to present concepts the human brain within limits is resistant to the effects of intrauterine deprivation". [24, p 884]

Studies by Munsinger [36] and Kamin [29] did not add any new data but pooled that of the earlier studies, very inaccurately in Munsinger's case. Kamin, correcting errors, found there was an IQ advantage to the heavier twin of around 5 IQ points which was independent of difference or similarity in BW. However, he falsely equates both Babson's [3] 25% weight difference category and Fujikura and Froelich's [24] 15% PDB group with his 300 g group, and his pooled data still suffers from the invalidities of different samples and IQ tests. He also denies that the effect found can be attributed to the TTS. Kamin [29] provides the only cotwin concordance rates in the BWD studies. The IQ "difference correlation" is 0.71 falling to 0.64 when cotwins of different BW are excluded. While these correlations are also from the pooled studies, numbers are still so low that correlations do not differ significantly.

James [28] demonstrates comprehensive knowledge of the TTS. He highlights Kamin's [29] faulty reasoning in assuming that the TTS has a deleterious effect only on the lighter donor and is independent of weight difference. He argues strongly that since live-born twins displaying the full clinical symptoms of the TTS are rare, the more superficial placental interconnections are the cause of the higher IQ in the heavier twin with BW being an index of the adequacy of blood supply. However, his paper provides no new data.

The only relevant new data appears to be a recent Australian study [34] and an unpublished study [21].

The former study [34] used 46 sets of twins aged 16-68 years for whom BW were available. It offered potential in providing new test data in the nonverbal area by using the Raven's Progressive Matrices on a larger sample with a wide age range and with monozygosity confirmed by "an exhaustive analysis of blood groups". However, while the raw data remains a valuable addition to what is presently available, the purpose was to use twins to demonstrate the existence of intrauterine effects on normal intelligence, seeing BWD as a crude indication of the relative favourableness or unfavourableness of such conditions. The methodology reflects poor understanding of the precise nature of these conditions and in particular of the TTS. It contains only 4 sets where one twin weighs more than 2,500 g and the other less. The rest are either both above or both below that weight and the groups were compared on that basis providing only a "suggestive" indication that the heavier twin in both the > and < 2,500 g groups scored better. No attempt was made to group the sample according to weight differences and to compare cotwins in each. Also claimed was that absolute weight did not appear to interact significantly with the effect of BWD within pairs, but no figures were provided to substantiate these findings. Reanalysis of existing data was poor compared to Kamin [29] and included own data. It indicated a significant difference in favour of the heavier group in all studies, but due to faulty method, such a reanalysis adds little to the weight difference literature.

In the unpublished study [21], 23 pairs of "mostly MZ" twins with a significant BWD (< 460 g) were compared with 23 controls with no BWD [21]. Amongst other issues, the question of whether initial BW difference is maintained and whether it effects performance on the Block Design Level (BDL) Test of the British Ability Scales (a test of spatial ability) and PPVT, was examined. The large weight difference group's mean performance level was significantly lower on BDL but did not differ on PPVT. However, the findings may not be valid since zygosity was not clear, the sample was small and the sexes mixed.

A different analytic approach to the problem was presented recently [5]. Five data sets from earlier studies were analysed to show that variance in IQ was greater in the lower scoring than in the higher scoring MZ cotwins. However, while emphasizing that the investigation was motivated by the unique prenatal circumstances of MZ twins, these were not specified.

Since large weight differences are a fairly reliable indicator of the presence of the TTS which can only occur in MC placentation and small weight differences may suggest DC placentation, research studies on chorionicity and intellectual development of MZ twins are relevant to this paper. With the exception of the most recent [41], a series of published papers [10,35,45] will be discussed in a later paper.

In summary, there are a number of findings and observations concerning MZ twins in these studies which are worthy of further investigation. Some of these are:

a) MZ twins with a PDB > 25% and below 2,000 g form a unique group probably affected by the TTS. The heavier twins in this group scored significantly better on the Stanford Binet and PPVT test [3].
b) The heavier twins scored better only on the Performance Scale of the WISC [15].
c) The smaller MZ twins scored lower in IQ in every case but there was no difference in the female sample [20].
d) Only in MZ pairs with BWD > 300 g was there an almost significant IQ difference in favour of the heavier twin [30].
e) Cotwins were more highly correlated in the large BWD group than in the smaller group [29].
f) The advantage to the heavier twin where PDB > 25% remained or even increased into adulthood but the smaller twin may attempt to compensate [4].
g) The concept of PDB and the tendency for heavier twins in the > 15% PDB to score higher [24].
h) The IQ advantage to the heavier twin is independent of difference or similarity in BW [29].

One of the aims of the present study was therefore to further investigate some of these earlier findings by including in its design:
a) accurate zygosity determination;
b) wide age range;
c) large sample size;
d) separate analysis of males and females;
e) percentage weight differences as well as absolute weight differences;
f) tests of separate cognitive abilities;
g) nonverbal and verbal tests;
h) cotwin concordance rates.

Unfortunately, placental data were not available for a sufficiently large sample to be included in the present study. However, relevant data are currently being sought from Melbourne hospitals, and the follow up testing of children for whom adequate data are obtained, particularly with respect to chorionicity, will form the subject of a later paper.

METHOD

Study Sample

Subjects were 100 sets of MZ twins (45 female, 55 male) selected from the children enrolled in the La Trobe Twin Study of Behavioural and Biological Development (LTS) who had been tested during the years 1978 to 1983 [26]. They were chosen on the basis of availability of information on BW, test scores and accurate zygosity. Zygosity was determined from blood-typing, photographs and the clinical judgement of the tester as well as by a zygosity questionnaire filled out by the parent. They were aged between 7 and 15 years with a mean age of 8 years.

Test Instruments

Behavioural tests were selected from the LTS battery [26] to represent both the verbal and nonverbal skills as well as reflecting any differences between the groups in hemispherical dominance since it has been suggested that twins may show atypical lateralization patterns. Peabody Picture Vocabulary Test (PPVT) and Digit Span Forwards (DSF) from the Wechsler Intelligence Scale for Children (WISC-R) are tests of verbal recognition and verbal sequential memory, respectively, for which the left cerebral hemisphere is usually dominant. Block Design Level (BDL) from the British Ability Scales and Knox Cube (KC) from the Queensland Test are tests of perceptual organization and spatial sequential memory for which the right hemisphere is normally dominant. Digit Span Backwards (DSB) from the WISC-R also measures sequential memory but probably involves both hemispheres and Block Design Power (BDP) from the BAS is largely a measure of perceptual speed (how quickly the Block Design problems are solved). Physical measures included birthweight and hand, foot and eye dominance. The laterality measures were obtained from at least three actions performed by the child with each of the hand, foot and eye as well as from scores on the Purdue Pegboard Test for handedness.

Test Procedure

Tests were administered at the children's home either in the specially equipped LTS study caravan or in a quiet room. Each twin was tested separately and cotwins by different testers. All testers were either psychologists or were trained and supervised by psychologists. Those children who were only 3-4 years at the last testing were tested again during 1986.

Analysis

Following the method of previous studies [23,24], difference in birthweight between cotwin was converted into percentage difference (PDB). As well, absolute difference in BW (ADB) was also used in some analysis because the level of weight difference at which the TTS operates is still fairly arbitrary [28] although a 25% PDB or more has been taken as indicating the presence of the TTS [40]. For comparability with Fujikura and Froelich's study [23] the sample was divided into four groups on the basis of size of PDB.

Since group D involved only small numbers, it was included with group C for most analyses. Mean performance of each group was determined using PDB groups mainly because their numbers were equable.

In earlier studies, only Kamin's pooled data [29] have presented cotwin correlations for large or small within-pairs weight difference groups, so results from the study were compared to the most recent study [41] on chorionicity and intellectual development. For this preliminary comparison, their MC group was equated with our largest WD Group (> 450 g) and their DC group to our smallest WD group (< 100 g), although the groups are obviously not fully interchangeable.

The sample was also grouped according to dominance: Group A including sets of twins who were both right dominant (RR); Group B those who were both left dominant (LL), and Group C where cotwins were mixed (LR) in two out of three of the measures of which one was handedness. The tests scores of this last mixed or "mirror-image" group was compared with the RR group for mean difference on ability measures and the left- and right-handed twins within the mirror image group were also compared in the same way.

RESULTS

Table 1 presents, for males and females separately, the mean BW for the heavier and lighter cotwins as well as their ADB and PDB.

Table 1. Mean birthweights for heavier and lighter cotwins, absolute difference birthweights (ADB), and percentage difference birthweights (PDB) for males and females

Group	No. of sets	MBW, heavier (g)	MBW, lighter (g)	ADB (g)	PDB (%)
Males	55	2654.2	2389.6	264.6	10.0
Females	45	2733.7	2408.6	325.1	11.9

All groups are close to what most other studies have found is the average BW for twins - around 2,500 g [17], although in an Aberdeen sample the twins were lighter [19]. The PDB for the whole sample is also comparable to previous findings which suggest an average of PDB 10% [28,40].

Table 2 compares absolute numbers and percentages in the 4 PDB groups (A,B,C,D) with an earlier study [24]. Both studies suggest a broad division of around 70% of the sample falling below 15 PDB and 30% falling above it.

The present study has a higher percentage in the extreme groups, the smallest and the largest PDB groups. In the earlier study, 54% of the sample fell into group B (PDB 6-15%) while in the present study the numbers in groups A & B are more equably distributed, with 38% in group B. In another study of DZ and MZ cotwins [22], 56.6% fell within 250 g of each other vs 60% of our MZ sample, although this represented 69% of the males but only 48% of the females. The same study reported that only 4% showed cotwin WD of over 750 g vs 14% in the present study. The difference could be partially explained by the fact that their 182 sets included both MZ and DZ twins, even though the DZ would be unlikely to be represented in this large WD group [24].

Table 3 provides a complete breakdown of the sample into PDB groups with group MBW as well as ADB and PDB presented for heavier and lighter twins by sex. For group D twins

Table 2. Sample distribution by percentage difference birthweight (PDB) group A, B, C, D, for present and earlier study [24]

Study		A (0-5)	B (6-15)	C (16-25)	D (26+)	Total
Fujikura	N	7	27	10	6	50
Froelich [24]	%	14	54	20	12	100
Present	N	33	38	15	14	100
study	%	33	38	15	14	100

Table 3. Mean birthweights (MBW), absolute difference birthweights (ADB), percentage difference birthweights (PDB) for heavier and lighter cotwins, males and females, groups A, B, C, D

	A			B			C			D		
	MBW (g)	ADB (g)	PDB (%)	MBW (g)	ADB (g)	PDB (%)	MBW (g)	ADB (g)	PDB (%)	MBW (g)	ADB (g)	PDB (%)
Males		*N = 20*			*N = 21*			*N = 7*			*N = 7*	
Heavier	2753			2517			2896			2543		
		64	2.3		210	8.3		548	18.9		718	28.3
Lighter	2689			2307			2348			1825		
Females		*N = 13*			*N = 17*			*N = 8*			*N = 7*	
Heavier	2661			2866			2743			2583		
		67	2.5		288	10.1		503	18.6		728	29.0
Lighter	2594			2578			2240			1845		

of both sexes, the lighter twins were more than 700 g lighter than the lighter twins in group A, a finding also highlighted by Fujikura and Froelich [24]. However, unlike this earlier study, the heavier twins in this large WD group were not larger than their counterparts in group A. The group MBW differences are fairly comparable between the sexes.

For the total sample, the twins are above average on all tests except Digit Span Backwards, a finding noted in other studies and attributed to poorer concentration in twins [27]. For this whole sample, as well as for the female group, there are no significant differences between the mean performance of the heavier and lighter cotwins. However, the scores are in the direction of the heavier twin having a similar or higher score on all tests except for Digit Span Forwards.

For the male sample, there are also no significant differences with the exception of BDL, where the heavier twins have the higher score by 2.4 points ($P < 0.02$). For the rest of the tests, where there are differences they are in the direction of the lighter twin having the higher score.

Results for mean scores of heavier and lighter twins by PDB groups are presented in Table 4 for males and females. For this analysis, groups A + B, C + D are combined. For group A + B males, only in DSF is there a significant difference and the scores again tend towards the lighter twin scoring better at everything. For the females in this group, the only significant difference is in PPVT where the heavier twin scores better.

When groups A + B twins are examined separately, there is no change in the pattern

Table 4. Comparison of mean differences between cotwins scores for small weight difference group (A + B), with scores for large weight difference group (C + D)

Test	Males		Females	
	df	Mean difference	df	Mean difference
Group A + B				
Digit Span				
Forward	37	-0.7**	25	0.0
Backward	37	0.0	25	0.2
Knox Cube	38	-0.4	28	0.9
Block Design				
Level	35	1.4	25	1.2
Power	34	3.8	25	1.6
PPVT	40	-0.1	27	5.8*
Group C + D				
Digit Span				
Forward	10	0.9	13	0.1
Backwards	10	0.1	13	-0.6*
Knox Cube	13	0.0	14	0.9*
Block Design				
Level	10	5.8***	11	1.1
Power	10	0.1	11	1.1
PPVT	13	-2.9	14	-1.0

Minus (-) indicates lighter twin scores better. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

of scores between the groups except for BDL where the difference between cotwins is not significant for group A males.

The most significant result is for group C + D males. In this large PDB group, the heavier twins are significantly better at BDL, the mean difference being 5.8 points ($P < 0.003$). While the heavier twins also tend to score better at Digit Span, they have the lowest KC score of all the male groups. The lighter twins in this group also tend to be better at PPVT.

For group C + D females, there are significant differences in DSB in favour of the lighter twins, and in KC in favour of the heavier. There is also a tendency for both male and female lighter twins in the large WD group to score better.

To summarize (Table 4) the results suggest that, except for the significant BDL difference in favour of the heavier males in the large PDB group, cotwin scores are not significantly different for most tests irrespective of BW difference. It is also clear that for this test (BDL), it is the lighter males among sets with a large cotwin weight difference who are at a significant disadvantage as it is their score which is depressed (rather than the heavier twin's score inflated). In the small WD group there is a tendency, except for BDL, for the lighter twin to score better.To see whether this significant finding in BDL held if WD between cotwins was increased, scores of both sexes were examined for WD above 460 ADB, 560 ADB and 25% PDB. It was found that, as weight difference increases, the scores of both male and female heavier twins and the lighter female twins remain similar (around 62 points) but the score of the lighter male twins decreases to 52.6 points for the > 25 PDB group.

Table 5 looks more closely at the BDL scores of this largest WD group. The individual scores of each of the 10 sets are presented and for males only, in every case, the lighter twins have the lower score. Such an ordering would not have occurred by chance ($P < 0.05$) on a binomial test.

Concordance rates (as expressed by cotwin correlations) are shown in Table 6 for all groups.

Across all groups cotwin correlations are more often significant for females and remain at a similar level across all tests and groups. For example, in group A, all cotwin test correlations are significant (around 0.70) for females. For males in the same group they are more variable < 0.60 to > 0.80 and DSB is not significantly correlated at all. With increasing weight difference, there is a tendency in the male sample towards greater intrapair concordance, which in group C is above 0.80 for all tests except DSF and BDP where the correlation is significant. It is also only in this group that the correlation for DSB reaches 0.89 ($P < 0.0001$), the second highest concordance rate for all groups. Except for group A females, this test only shows a significant cotwin correlation in large WD males and females. The highest correlation of 0.92

Table 5. Individual scores, Block Design Level, > 25% weight difference group

Set	Males		Females	
	Heavier	Lighter	Heavier	Lighter
1	68	56	69	66
2	60	56	67	67
3	46	33	57	57
4	73	63	67	56
5	58	55	60	73

Table 6. Significant cotwin correlations, groups A, B and C + D for all tests, males and females

Test		DSF	DSB	KC	BDL	BDP	PPVT
A	Male	0.80*** (19)	NS	0.62*** (19)	0.69*** (18)	0.86*** (17)	0.56** (20)
	Female	0.77** (12)	0.73** (12)	0.73** (13)	0.75** (12)	0.52* (12)	0.74** (13)
B	Male	NS	NS	0.67*** (20)	0.80** (18)	NS	0.51** (21)
	Female	0.70** (14)	NS	0.81*** (16)	0.79*** (14)	0.72** (14)	0.75** (15)
C+D	Male	NS	0.89*** (11)	0.80*** (14)	0.92*** (11)	NS	0.84*** (14)
	Female	0.72** (14)	0.79*** (14)	0.79*** (15)	NS	NS (15)	0.66**

* $P < 0.05$; ** $P < 0.01$; ***$P < 0.001$, NS: not significant.

($P < 0.0001$) is for BDL and again occurs in the large weight difference males (group C + D). However, for group C + D females, BDL is not significantly correlated at all and the concordance rate for PPVT is also lower than for the group C + D males.

Overall, on the four ability tests in which cotwin correlations reach significance, DSB, KC, BDL and PPVT, this large PDB male group is more concordant than any other group. Unlike the large PDB female group, the cotwin correlation is not significant for DSF.

Table 7 presents the number of sets who were RR, LL or RL. In this sample, 19% of the children are left-handed. This is significantly more than the 6% incidence in the general population and is in agreement with researchers who claim there is a higher incidence of left-handedness in twins [43].

The mean birthweight of the RL "mirror-image" twins was not significantly different from the concordant group. However, the mean BWD is greater for the mirror image group.

Within the mirror image group, the left-handed twin was not significantly more often the lighter (donor) twin for either males or females. In terms of PDB group for both males and females it can be seen from Table 8 that there is an equable distribution throughout groups A + B of around 30% "mirror image" within each group. In contrast, for the males, there

Table 7. Laterality in total sample, males, and females

	Dominance		
	RR	LL	RL
Total sample (N)	68	2	30
Males (N)	37	1	17
Females (N)	31	1	13

Table 8. PDB group membership - "mirror-image" twins

	Group			
	A	B	C	D
Males	N = 20	N = 21	N = 7	N = 7
No. mirror-image	4	6	4	4
% mirror-image	20	29	56	57
Females	N = 13	N = 17	N = 8	N = 7
No. mirror-image	4	5	4	-
% mirror-image	30	29	50	0

are proportionately more "mirror image" twins in group C + D and percentage within each group increases from 20% to 57%. For females, it also increases to 50% in group C but there are no "mirror-image" twins in group D.

The mean scores of the right- and left-handed twins in this group were not significantly different on any test including Block Design Level. Even within group C the mean scores of the right-handed and left-handed twins were identical with the lighter twin being right-handed in three cases and left-handed in three.

Table 9 shows group concordance rates for Rose et al's study [42] and the present one are similar for PPVT but not for Block Design. Their lower concordance rate for DC twins on this test does not concur with the results of our sample where males and females are combined but is what has been found for male twins only.

Table 9. Cotwin correlations for large and small weight difference groups for PPVT and Block Design - comparison with earlier study of MC and DC, MZ twins [41]

	MC-MZ [41]	>460 g PDB	DC-MZ [41]	<100 g PDB
PPVT	0.95 N = 17 P< 0.001	0.72 N = 22 P < 0.001	0.95 N = 15 P < 0.001	0.71 N = 23 P < 0.001
Block Design	0.92 N = 17 P < 0.003	0.73 N = 18 P < 0.001	0.48 N = 15 P < 0.09	0.70 N = 22 P < 0.000

DISCUSSION

This study does suggest an effect of cotwin weight differences mainly on nonverbal abilities in male twins and in particular those tapped by the Block Design Level Test and Digit Span Backwards. The lighter twin, usually but not invariably the donor [29], is significantly disadvantaged in the cognitive functioning tapped by the BDL test where there is a large cotwin weight difference.

The reasons for this are not clear and can only be discovered by further research. They could possibly relate to differences in brain functioning resulting from late splitting or from differences in nutrition or blood supply, as a result of the twin transfusion syndrome [2,8].

With respect to the former hypothesis of differences in lateralization, this preliminary examination is only a small beginning. In this sample, "mirror imaging" is related to the presence of the TTS, as indicated by large weight differences only for male twins with large PDB's and is not related in females. It can also occur in twins with very small cotwin weight differences: 20% of the present sample who showed this mixed dominance fell below the 15% PDB level and 8 sets (4 male, 4 female) were in the smallest PDB group. In contrast, Hay and Howie [25] found all their MZ twins who were of mixed handedness fell into the group with BWD above 450 g. However, their sample was small (only 16 MZ sets) and the authors suggested further verification was needed concerning the relationship between the TTS and handedness in MZ twins. More direct measures of hemispheric specialization such as dichotic listening are necessary in addition to larger samples.

It would appear that the relationship between time of split, TTS, and cotwin WD is not a simple one. The presence of the syndrome may be indicated by large cotwin weight differences as can later splitting, defined as after 3-4 days. However, "mirror imaging" may not be as closely related to later zygote division as would seem plausible, except if "mirror image" twins with small cotwin weight differences were MC twins who have not experienced the TTS. Only placental data could clarify this.

In addition, while there is a relationship between severity of the TTS and "spatial" ability for males, the deficit is not caused by whatever factors (eg, greater stress) produce left handedness in twins. The donor twin is not the more likely to be the left-handed one of the pair.

In terms of a biological explanation, a few studies offer some possible supporting evidence for the finding of a lower cotwin concordance in small BW difference groups which could warrant further investigation. Corey et al [16] observed that members of DC MZ pairs tend to be more discordant in blood cholesterol content than members of MC pairs, commenting that

> "It seems plausible that any such development asynchrony would tend to be minimized in monochorionic twins by the presence of a single placenta and circulatory anastomosis, but not in dichorionic twins because of their physical and/or circulatory separation which allows each twin to develop at a more nearly independent rate". [16, p 439]

In addition, the same researchers found a sex difference in the mean cord blood cholesterol levels of newborn MZ twins in favour of males. Still, the explanation for the sex differences in the present study remains unknown.

It has also been suggested [18] that a study of hemoglobin levels [12] elucidates further the mechanisms operating in the TTS. In a sample of affected pairs at the Hammersmith Hospital in London, Bryan found in the 7 pairs of MZ twins where there was an intrapair difference in hemoglobin concentration of 5 g/100 ml there were substantial differences in cotwins in Immunoglobulin G (IgG) and it was the lighter donor twin who was affected.

In summary, the results of this study suggest that:

a) Males and females are differentially affected by the mechanisms causing large birthweight differences between MZ cotwins.
b) These differences may be masked if male and female twins are not analysed separately.
c) The lighter male cotwins with large birthweight differences are disadvantaged in the brain

functioning tapped by the Block Design Level Test.

d) The concordance rate for the male cotwins with large birthweight differences is higher than for those who are female or of a smaller birthweight difference.
e) Mixed dominance occurs in both early and late splitting twin pairs.
f) Where there is a large cotwin weight difference, male twins only are likely to be of mixed dominance.
g) The donor twin is not more likely to be the left-handed twin in the pair.
h) There is no difference between right-and left-handed MZ twins in their scores on the ability tests administered in this study.

Obviously, there is a need for more extensive testing of larger samples, particularly in the large weight difference group, as well as for the employment of a more extensive battery of "spatial tests". Nevertheless, there would still be a serious drawback to using weight differences to examine the long-term effects of intrauterine conditions because the origin of these differences with respect to placental form is ambiguous. Weight differences cannot alone indicate form of chorionicity. While large cotwin differences certainly suggest monochorionicity as very few DZ twins show weight differences over 25% [24], they could also arise where cotwins had two placentas of differing efficiency causing independent intrauterine growth.

Future research requires samples for whom not only BW differences but also chorionicity are known. In the words of MacGillivray "MC twins are smaller and have a greater intrapair variation in birth weight than DC twins. It is thought that the most important factor in the intrapair variations of MZ twins is the unequal exchange of plasma proteins". [33, p 151]

Ultimately, the extent and prenatal causes of the differences between MZ twins in intellectual ability will depend on further investigation using twins for whom thorough placental examinations were made by a pathologist at birth. To date this critical prenatal information has not been available for most twin children. For a period, twin placentas were routinely examined by a pathologist at two Melbourne hospitals and children for whom we have this necessary data are now up to 16 years old. The follow-up testing program presently in progress has been carefully designed to overcome the earlier problems of studies described in this paper and should clarify the relationship between specific prenatal conditions and the intellectual ability of MZ twins. It will also provide further evidence against the validity of any assumption of developmental equivalence between MZ and the general population.

Abbreviations: ADB = absolute difference birthweight; BDL = Block Design Level; BDP = Block Design Power; BW = birthweight; BWD = birthweight difference; DC = dichorionic; DSF = Digit Span Forward; DSB = Digit Span Backwards; DZ = dizygotic; KC = Knox Cube; MC = monochorionic; MZ = monozygotic; PDB = percentage difference birthweight; PPVT = Peabody Picture Vocabulary Test; TTS = twin transfusion syndrome; WD = weight difference; WISC = Wechsler Intelligence Test for Children.

REFERENCES

1. Abraham JM (1967): Intrauterine feto-fetal transfusion syndrome - Clinical observations and speculations on pathogenesis. Clin Pediatr 6:405-410.
2. Aherne N, Strong SJ, Corney G (1968): The structure of placenta in the twin transfusion syndrome. Biol Neonatol 12:121-135.
3. Babson SG, Kangas J, Young N, Bramhall L (1964): Growth and development of twins dissimilar in size at birth. Pediatrics 33:327-333.

4. Babson SG, Phillips DS (1973): Growth and development of twins dissimilar in size at birth. New Engl J Med 289:937-940.
5. Bailey MJ, Horn JM (1986): A source of variance in IQ unique to the lower scoring monozygotic (MZ) co-twin. Behav Genet 16:509-516.
6. Benirschke K (1961): Examination of the placenta - accurate recording of twin placentation - a plea to the obstetrician. Obstet Gynecol 18:309.
7. Benirschke K, Driscoll SG (1967): The Pathology of the Human Placenta. New York: Springer Verlag.
8. Benirschke K, Kim CK (1973): Multiple pregnancy Part I - II. New Engl J Med 288:1276-1284, 1329-1336.
9. Boklage CE (1981): On the timing of MZ twinning events. In Gedda L, Parisi P, Nance WE (eds): Twin Research 3. Part A. New York: Alan R. Liss, pp 155-165.
10. Brown B (1977): Placentation effects on birth-weight and IQ in MZ twins. Paper presented at the meeting of Society for Research in Child Dev., New Orleans.
11. Bulmer MG (1970): The Biology of Twinning in Man. Oxford: Clarendon Press.
12. Bryan EM (1977): IgG deficiency in association with placental oedema. Early Hum Dev 1:133-143.
13. Bryan EM (1983): The Nature and Nurture of Twins. London: Bailliere Tindall.
14. Cameron AH (1968): The Birmingham Twin Survey. Proc Roy Soc Med 61:229- 234.
15. Churchhill JA (1965): The relation between intelligence and birth-weight in twins. Neurology 15:341-347.
16. Corey LA, Nance WE, Kang KW, Christian JC (1979): Effects of type of placentation on birth-weight and its variability in monozygotic and dizygotic twins. Acta Genet Med Gemellol 28:41-50.
17. Corney G, Robson EB, Strong SJ (1972): The effect of zygosity on the birthweight of twins. Ann Hum Genet 36:45.
18. Corney G (1978): Twin placentation and some effects on twins of known zygosity. In Nance WE, Allen G, Parisi P (eds): Twin Research: Biology and Epidemiology. New York: Alan R Liss, pp 9-16.
19. Corney G (1979): The effect of zygosity on birth-weight of twins in Aberdeen and NE Scotland. Acta Genet Med Gemellol 28:353-360.
20. Drillien CM (1970): The small for date infant: Etiology and prognosis. Pediatr Clin North Am 17:9-24.
21. Foley D (1983): The effect of the feto-fetal transfusion syndrome in monozygotic twins on later physical and mental development. Unpublished report, La Trobe University, Australia.
22. Friedman EA, Sachtleben MS, Friedman LM (1977): Relative birthweight in twins. Obstet Gynecol 49:717-720.
23. Fujikura T, Froehlich LA (1970): Twin placentation and zygosity. Obstet Gynecol 37:34-43
24. Fujikura T, Froelich LA (1974): Mental and motor development in MZ co-twins with dissimilar birth-weights. Pediatrics 53:884-889.
25. Hay DA, Howie PM (1980): Handedness and differences in birthweight in twins. Perceptual and Motor Skills 51:666.
26. Hay DA, O'Brien PJ (1981): The interaction of family attitudes and cognitive abilities in the La Trobe study of behavioural and biological development. In Gedda L, Parisi P, Nance WE (eds): Twin research 3. Part B. New York: Alan R. Liss, pp 235-250.
27. Hay DA, O'Brien PJ (1983): The La Trobe Twin Study: a genetic approach to the structure and development of cognition in twin children. Child Dev 54:317-330.
28. James WH (1982): The IQ advantage of the heavier twin. Br J Psych 73:513- 517.
29. Kamin LJ (1978): Transfusion syndrome and the heritability of IQ. Ann Hum Genet 42:161-171.
30. Kaebler GT, Pugh JF (1969): Influence of intrauterine relations on the intelligence of the twins. New Engl J Med 280:1030-1040.
31. Kaebler CT, Pugh TF (1969): Erratum. New Engl J Med 281:332.
32. MacGillivray I, Nylander P, Corney G (1975): Human Multiple Reproduction. London: WB Saunders Co.
33. MacGillivray I (1978): Twin pregnancies. In Obstetrics and Gynaecology Annual, 135-151.
34. Marsh RW (1980): The significance for intelligence of differences in birth-weight and health within monozygotic twin pairs. Br J Psych 71:63- 67.
35. Melnick M, Myrianthopoulos NC, Christian JC (1978): The effect of chorion type on variation in IQ in the NCPP twin population. Am J Hum Genet 30:425-433.
36. Munsinger H (1971): The identical twin transfusion syndrome. A source of error in estimating IQ resemblance and heritability. Hum Genet 40:307-321.
37. Nylander PPS (1969): The value of the placenta in the determination of zygosity - A study of 1,052

Nigerian twin maternities. J Obstet Gynaecol Br Commonw 76:699-704.
38. Potter EL (1963): Twin zygosity and placental form in relation to outcome of pregnancy. Am J Obstet Gynecol 87:566-577.
39. Price B (1950): Primary biases in twin studies: A review of prenatal and natal difference-producing factors in monozygotic pairs. Am J Hum Genet 2:293-352.
40. Rausen AR, Seki M, Strauss K (1965): Twin transfusion syndrome. A review of 19 cases studied at one institution. J Pediatr 66:613-628.
41. Rose R, Uchida I, Christian JC (1981): Placentation effects on cognitive resemblance of adult monozygotes. In Gedda L, Parisi P, Nance WE (eds): Twin Research 3. Part B. New York: Alan R Liss, pp 37-41.
42. Scarr S (1969): Effects of birth-weight on later intelligence. Soc Biol 16:249-256.
43. Springer SP, Searleman A (1980): Left handedness in twins: implications for the mechanisms underlying cerebral assymmetry of function. In Herron J (ed): Neuropsychology of lefthandedness. New York: Academic Press.
44. Strong SJ, Corney G (1967): The Placenta in Twin Pregnancy. Oxford: Pergamon Press.
45. Welch P, Black KN, Christian JC (1978): Placental type and Bailey mental development score in 18-months-old twins. In Nance WE, Allen G, Parisi P (eds): Twin Research 3: Psychology and Methodology. New York: Alan R Liss, pp 145-149.
46. Yoshida K, Soma H (1984): A study of twin placentation in Tokyo. Acta Genet Med Gemellol 33:115-120.

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