Journal of the International Neuropsychological Society (2016), **22**, 865–877.

doi:10.1017/S1355617716000758

Neuropsychological Functioning in Preterm-Born Twins and Singletons at Preschool Age

Sarah Raz,[1] Jamie C. Piercy,[1] Andrew M. Heitzer,[1] Brittany N. Peters,[1] Julie Bapp Newman,[2] Angela K. DeBastos,[1] Noa Ofen,[1,3] Beau Batton,[4] and Daniel G. Batton[4]

[1]Department of Psychology and the Merrill Palmer Skillman Institute, Wayne State University, Detroit, Michigan
[2]Division of Pediatric Neuropsychology, Children's National Medical Center, Washington, District of Columbia
[3]The Institute of Gerontology, Wayne State University, Detroit, Michigan
[4]Department of Pediatrics, Southern Illinois University School of Medicine, Springfield, Illinois

(Received April 14, 2016; Final Revision July 14, 2016; Accepted August 12, 2016)

Abstract

Objectives: A limited body of research is available on the relationships between multiplicity of birth and neuropsychological functioning in preterm children who were conceived in the age of assisted reproductive technology and served by the modern neonatal intensive care unit. Our chief objective was to evaluate whether, after adjustment for sociodemographic factors and perinatal complications, twin birth accounted for a unique portion of developmental outcome variance in children born at-risk in the surfactant era. **Methods:** We compared the neuropsychological functioning of 77 twins and 144 singletons born preterm (<34 gestational weeks) and served by William Beaumont Hospital, Royal Oak, MI. Children were evaluated at preschool age, using standardized tests of memory, language, perceptual, and motor abilities. **Results:** Multiple regression analyses, adjusting for sociodemographic and perinatal variables, revealed no differences on memory or motor indices between preterm twins and their singleton counterparts. In contrast, performance of language and visual processing tasks was significantly lower in twins despite reduced perinatal risk in comparison to singletons. Effect sizes ranged from .33 to .38 standard deviations for global language and visual processing ability indices, respectively. No significant group by sex interactions were observed, and comparison of first-, or second-born twins with singletons yielded medium effect sizes (Cohen's $d = .56$ and .40, respectively). **Conclusions:** The modest twin disadvantage on language and visual processing tasks at preschool-age could not be readily attributable to socioeconomic or perinatal variables. The possibility of biological or social twinning-related phenomena as mechanisms underlying the observed performance gaps are discussed. (*JINS*, 2016, *22*, 865–877)

Keywords: Neonatal prematurity, Birth weight, Birth order, Language development, Visual perception, Motor skills

INTRODUCTION

The developmental outcome of twins has been the subject of research endeavors for nine decades, with increasing interest following the dramatic rise in multiple gestation since the 1970s (Gucuyener et al., 2011). Based on meta-analysis of studies comparing intellectual outcome of multiples and singletons over 8 decades (1924–2008), Voracek and Haubner (2008) concluded that on average, twins obtained 4.2 IQ points below singletons in childhood or adolescence. Similarly Thorpe (2006), who systematically examined a similar body of literature in the language domain, found that mild language delays are prevalent and consistently observed in twins. Because multiples are more likely than singletons to experience perinatal complications (ESHRE Capri Workshop Group, 2000; Lorenz, 2012; Papiernik et al., 2010), Voracek and Haubner (2008) speculated that the factor accounting for poorer performance in twins could be the increased frequency of complications such as suboptimal intrauterine growth and preterm birth.

To meaningfully study the early biological factors that might adversely influence developmental outcome in multiples, one should use an appropriate singleton comparison group, with sufficient consideration for gestational age. Approximately 10% of preterm births (<37 weeks gestation) in the United States are attributable to twins, whereas premature twins comprise >50% of all U.S. twin births (Martin, Hamilton, & Osterman, 2012; Martin, Hamilton,

Correspondence and reprint requests to: Sarah Raz, Developmental Neuropsychology Laboratory, the Merrill-Palmer Skillman Institute, Wayne State University, 71 E. Ferry, Detroit, MI 48202. E-mail: sarahraz@wayne.edu

Ventura, et al., 2012). Approximately 11% of twins are very preterm (<32 weeks; Martin, Hamilton, Ventura, Osterman, & Mathews, 2013). Thus, comparison of neuropsychological functioning between preterm-born twins and their singleton counterparts is essential for teasing apart the effects of twinning from influences associated with perinatal risk.

Bodeau-Livinec et al. (2013) noted that performance deficits observed in term-born twins, compared to term-born singletons, are not easily generalizable to a population of preterm-born twins, compared to their preterm singleton counterparts. Reduced generalizability is expected because, in the preterm population, both twins and singletons are at increased risk for ante-, peri-, and neonatal complications. Yet in term-born cohorts, twins would be at substantially increased risk for medical complications. Because of recent advancements in fertility treatment, conclusions based on the entirety of the 8-decade body of research reviewed by Voracek and Haubner (2008) or Thorpe (2006) may not apply to recent birth cohorts. Indeed, Voracek and Haubner reported a substantial difference between "less *versus* more recent" birth cohorts (5.1 *vs*. .5 IQ point discrepancy, respectively).

Whereas fertility treatment does not appear to alter developmental outcome (Yeung et al., 2016), a birth cohort effect may be explained, in part, by changes occurring in the composition and nature of the population of multiples available for study in industrialized nations following the introduction of assisted reproductive technology (ART). Although an overall increase in the rate of twin gestation has been attributed to the introduction of these technologies (Zork, Biggio, Tita, Rouse, & Gyamfi-Bannerman, 2013), the nonuniform and reduced availability of comprehensive statewide-mandated health insurance coverage of ART produced regional differences (Sunderam et al., 2015), and likely discrepancies between socioeconomic strata, in access to these treatments (Smith et al., 2014). Hence, earlier findings may not be generalizable to cohorts born in the last two and a half decades.

In addition to changes introduced by fertility treatments, children born preterm since the 1990s, whether twins or singletons, have benefited from advances in neonatal care such as surfactant therapy, gentler mode of mechanical ventilation, and antenatal glucocorticoid therapy (Jobe & Bancalari, 2001). However, few surfactant-era investigations included comparisons of neuropsychological outcome between preterm twins and singletons. Of eight such investigations, six used infancy developmental measures. Four of these studied preterm and/or very preterm samples (Asztalos, Barrett, Lacy, & Luther, 2001; Eras et al., 2013; Kyriakidou, Karagianni, & Iliodromiti, 2013; Manuck, Sheng, Yoder, & Varner, 2014), while the remaining two focused on extremely preterm (gestational age < 28 weeks), or extremely low birth weight (<1000 g), infants (Hajnal, Braun-Fahrlander, von Siebenthal, Bucher, & Largo, 2005; Wadhawan et al., 2009). Group differences were reported in only one of the six infancy studies (Wadhawan et al., 2009), yet the investigators incorporated infant demise in their composite index of impairment. Of the two investigations of preschool-age children (Bodeau-livinec et al., 2013; Einaudi et al., 2008), only the latter study reported outcome differences in favor of singletons, using a global measure of cognitive ability.

While reports of developmental outcome differences between first-, or second-born twins and their singleton counterparts are uncommon, in several studies increased risk for respiratory complications (Arnold, McLean, Kramer, & Usher, 1987; Hacking, Watkins, Fraser, Wolfe, & Nolan, 2001) or composite perinatal and neonatal complications (Armson et al., 2006) was documented in the second-born (nonpresenting) twin regardless of delivery route. A recent investigation of early school-age children revealed a first-born twin advantage in neuropsychological outcome among preterm-born male twins (Gonzalez-Mesa, Cazorla-Granados, & Gonzalez-Valenzuela, 2016).

In contrast with earlier studies of preterm twins and singletons, in this investigation we examined the associations between multiplicity (plurality) and outcome in several domains of neuropsychological functioning, including memory efficiency, language abilities, visual processing, and motor skills. In particular, we hypothesized that multiplicity will account for a unique portion of developmental outcome variance, over and above the variance explained by sociodemographic or perinatal factors that may confound the effects of twin birth. Because adverse outcome effects of multiplicity may be more pronounced in boys (Gucuyener et al., 2011), and since sex differences may be more prominent in the language domain (Thorpe, 2006), we predicted that the strength of associations between multiplicity and neuropsychological outcomes will depend on "sex," perhaps more so in language functioning than in other domains. In addition to the above-listed hypotheses, we predicted poorer neuropsychological outcome in second-born twins, compared to their singleton counterparts.

METHOD

Participants

To examine the relationships between multiplicity of birth and neuropsychological outcome in preterm-born children, we evaluated products of either singleton or twin pregnancies at preschool-age. The children were born between 23 and $33^{6}/_{7}$ weeks gestation at William Beaumont Hospital (WBH), Royal Oak, Michigan, and treated in the neonatal intensive care unit (NICU). Children who had been transferred from other hospitals were excluded. WBH catchment area includes primarily middle socioeconomic strata. The children were born between 1996 and 2001 and evaluated between 3 and 6 years of age adjusted for prematurity. Children who had been diagnosed with congenital anomalies, or who continued to require mechanical ventilation after discharge, were not considered for recruitment.

The approach to extremely preterm infants at WBH was consistent throughout the study period. All infants assessed by the neonatologist to have a reasonable chance to survive based on the information available at the time of delivery received initial life-sustaining care after birth, including endotracheal intubation in the delivery room, if needed. Active intervention was administered to extremely preterm infants, with survival rate at the threshold of viability (23 weeks) reaching 40%. Approximately 87% of these survivors were free from sonographic evidence of severe brain injury (large IVH, intraparenchymal hemorrhage, or cystic PVL), as detailed in Batton, DeWitte, and Pryce (2011). The results from WBH NICU for the period of the current study are consistent with reports of extremely preterm infant outcomes from more recent cohorts (see Rysavy et al., 2015).

Eighty-one twins (28.02% of the total relevant 1996–2001 twin birth cohort) and 152 singletons (24.91% of the total relevant singleton birth cohort) were available for this investigation. However, since we were interested in studying the unique contribution of multiplicity to developmental outcome, we excluded eight singletons and four twins with neurological disorder or evidence of moderate/severe perinatal CNS injury. Of the eight singleton cases, two were diagnosed with moderate perinatal intraventricular hemorrhage (IVH), with CP diagnosed subsequently in one case. Two additional cases were diagnosed with hydrocephalus and four suffered severe perinatal IVH and/or parenchymal lesions.

Of the four excluded twins, three were diagnosed with severe perinatal IVH and subsequent CP, whereas one case manifested language difficulties of sufficient magnitude to preclude language assessment. In sum, following exclusion of cases diagnosed with congenital anomalies, cerebral palsy, or perinatal intracranial pathology (except mild IVH), and cases discharged on mechanical ventilation, the final sample included 144 singletons and 77 twins, 3–6 years of age, and born < 34 weeks gestation at WBH. None of the participants was disabled, with a single exception of a singleton with mild spastic diplegia and above-average intellectual performance who was retained in the sample. Altogether, approximately 20% of the study participants were extremely preterm (<28 weeks) with approximately 10% < 25 weeks estimated gestation.

Of the 221 participants remaining following exclusion of 12 "neurological" cases, 184 were recruited through an ongoing prematurity follow-up study (123 singletons and 61 twins) and 37 through an IVH outcome study (21 singletons and 16 twins). The selection criteria were similar for both studies, although the age range and participation rates were slightly different (4–6 years for the prematurity follow-up, 3–5 years for the IVH study, respectively; participation rates 64% and 56% of contactable families, respectively). Across the two studies, reason for non-participation was not provided in 51.51% of the cases whose families declined participation. Explanations offered for remaining cases were lack of time (19.39%) or interest in driving to Detroit (8.48%), testing not deemed essential (13.33 %), child unable to cooperate due to severe impairments (4.84%), and English not primary language (2.42%). Regardless of recruitment mechanism, there were no significant differences in the singletons to twins ratio of preschoolers obtained from the two studies for the current investigation (Yates corrected $\chi^2[1] = .93$; $p = .324$).

Eighteen of the twins were products of monochorionic, and 54 of dichorionic, placentation, according to pathology reports. For five cases, information about chorionicity was unavailable. Of the 77 twins, 23 were born following fertility treatment (11 *in vitro* fertilization, six clomiphene, and six miscellaneous other methods). Altogether, 68 twins were members of 34 pairs, with the remaining nine cases (3 first-, 6 second-born) lacking a tested co-twin. In one of the nine cases the co-twin died at birth, in two cases the co-twin had cerebral palsy (CP), while a single co-twin was unable to complete testing because of language impairment. In five additional cases, co-twins were not scheduled for evaluation by their family for unknown reasons. Little information is available to us approximately four of these five cases, while the remaining co-twin was the donor twin from a set diagnosed with twin-to-twin transfusion syndrome (TTTS). In addition to the recipient co-twin, the sample included a set of twins with TTTS diagnosis.

According to maternal report, none of our participants had sustained a head injury with loss of consciousness. History of at least one seizure was reported for nine cases (seven singletons, two twins), yet only one case, a singleton with petit mal diagnosis, was managed with medication during the evaluation. According to parental report none of the children had significant prenatal alcohol exposure (> a glass per day), although nicotine exposure (1–20 cigarettes per day) was reported for 27 cases.

Testing Procedures and Neuropsychological Assessment

Before the beginning of testing, informed consent was obtained from the attending parent/legal guardian(s), typically the mother, for each participant. All testing and other data collection procedures were conducted in accordance with the Helsinki Declaration and in compliance with the regulations of the Human Investigation Committee of WBH and the Institutional Review Board of Wayne State University.

Children were evaluated in one or two sessions, based on the examiner's assessment of the child's attention. The examiners were graduate students trained extensively in developmental neuropsychological assessment. Although they were informed about the participants' history of premature birth, they were kept unaware of the children's specific ante-, peri-, and neonatal complications. Memory skills were assessed using the Woodcock-Johnson (W-J) III Tests of Cognitive Abilities (Woodcock, McGrew, & Mather, 2001) Long Term Retrieval (LTR) domain score and constituting subtests, Visual Auditory Learning (VAL), and Retrieval Fluency (RFL). The broad ability of long-term retrieval (Glr cluster) involves the cognitive processes of acquiring, storing, and retrieving information and reflects the efficiency with which information is initially stored and later retrieved.

Whereas VAL is a test of associative memory that requires paired-associative encoding, storage, and retrieval, RFL is a test of ideational fluency and naming facility, requiring recognition, fluent retrieval, and oral production of examples of a semantic category (Schrank, 2011). We used the Preschool Language Scale (PLS-3; Zimmerman, Steiner, & Pond, 1992) to evaluate language skills. This standardized instrument includes a Total Language scale (TL), comprised of two subscales assessing receptive and expressive language: Auditory Comprehension (AC) and Expressive Communication (EC), respectively. The test includes tasks assessing semantic, morphological, syntactic, integrative language, and pre-literacy, linguistic competencies.

Assessment of visual processing was accomplished with the W-J III Picture Recognition (PR) subtest, which is one of the two tests that create the Gv, a cluster indexing visual-spatial thinking, that is, the extraction of features from visual stimuli. Such extraction includes the processes involved in generating, storing, retrieving, and transforming visual images (Schrank, 2011). Motor skills were assessed using the Peabody Developmental Motor Scales (PDMS-2; Folio & Fewell, 2000). This instrument, normed on a large stratified sample, is a comprehensive, standardized measure of motor skills that includes a Total Motor scale (TM) comprised of Fine and Gross Motor subscales (FM and GM, respectively).

General Statistical Considerations

To evaluate the effects of multiplicity on neuropsychological outcome, we used multiple regression analyses. The predictor of interest was the grouping factor, singleton *versus* twin birth (multiplicity). The predicted variables were the standard scores for the LTR domain and its components (VAL and RTF) in analyses of memory efficiency, the TL scale and its constituting subscales (AC and EC) in analyses of language abilities, the PR subtest in analyses of visual processing, and the TM scale with its constituting subscales (FM and GM) in analyses of motor skills. We included sociodemographic predictors, SES (Hollingshead, 1975), and sex, in all analyses.

To account for early medical risk, we selected three covariates: birth weight, the intrauterine growth *Z*-score, and the total complication score. Because gestational age and birth weight are highly correlated (Pearson $r[219] = .826$; $p < .001$ in our sample), we chose only the latter predictor to reduce collinearity. We reasoned that while the gestational-age range in our sample was truncated at $33^6/_7$ weeks, birth weight range was not limited, representing a naturally occurring spectrum within the preterm cohort of origin. Furthermore, birth weight, a variable reflecting perinatal differences within twin-pairs that are not captured by gestational age, is essential in comparing the first *versus* second-born twins to their singleton counterparts. The intrauterine growth *Z*-score was defined as the deviation of an infant's birth weight from the sex-specific mean weight of his/her gestational age group, in accord with norms published by Kramer et al. (2001). Before all analyses, we examined the interactions between each of the two dichotomous predictors (sex, multiplicity) and each continuous variable in the models. As none of the interactions were found to be significant, the reduced models were used instead.

To ensure independence of observations, and particularly since antenatal characteristics were shared by co-members of twinships, either the first- or second-born twin was randomly excluded from each of the 34 pairs of co-twins using a web-based random number generator (stattrek.com). Thus, together with the nine cases whose co-twin was not available or appropriate for this investigation, the reduced twin group was comprised of 43 members from separate pairs who were compared with the 144 singletons (Table 4). These analyses were followed by comparisons of the first- (Table 5), and second-born (Table 6) twin groups with the singletons. When significant relationships between predictors and global outcome measures were found, follow-up analyses of associations between predictors and subscale/subtest- performance were conducted using Bonferroni-corrected α levels, with familywise adjustments within outcome domains.

RESULTS

The proportions of boys and girls in the singleton and twin groups comprising our final sample, as presented in Table 1, were not significantly different from the proportions observed in the remaining singletons (57.08% males) and twins (50.47% males) from the relevant NICU birth cohorts (Yates corrected $\chi^2[1] = .374$; $p = .541$ and $\chi^2[1] = .081$; $p = .776$, for singletons and multiples, respectively). The proportions of African Americans in the singleton and twin groups comprising our final sample (Table 1) were 9.03% and 5.19%, respectively (Yates corrected $\chi^2[1] = .344$; $p = .557$). These proportions were not significantly different from the proportions observed in the singletons (10%) and twins (6.92%) from the remaining NICU cohort (Yates corrected $\chi^2[1] = .082$; $p = .775$ and $\chi^2[1] = .189$; $p = .663$, for singletons and twins, respectively).

Intrauterine growth restriction (IUGR) rates did not differ between participating *versus* nonparticipating singletons (12.5% *vs.* 15.88%, Yates corrected $\chi^2[1] = .735$; $p = .39$) or twins (7.79% *vs.* 8.49%, Yates corrected $\chi^2[1] = .003$; $p = .96$). Means ($\pm SD$) for gestational age and birthweight in our sample's singleton group (30.08 ± 2.83 weeks and 1436 ± 555 g, respectively) were similar to values observed for the total NICU singleton cohort (29.8 ± 2.8 weeks and 1454 ± 522 g, respectively). Similarly, the twin group means for the same two perinatal characteristics (30.16 ± 2.61 weeks and 1432 ± 480 g, respectively) resembled values observed for the total NICU twin cohort (30 ± 2.6 weeks and 1451 ± 457 g, respectively).

Tables 1–3 provide background sociodemographic and perinatal characteristics for the first-, and second-born twins. As Table 1 reveals, twins were characterized by higher SES, yet no other sociodemographic differences emerged. The observed group differences in SES are consistent with recent demographic trends in industrialized countries (Smith et al., 2014)

As shown in Table 2, the total number of ante-, peri-, and neonatal complications was significantly greater in the

https://doi.org/10.1017/S1355617716000758 Published online by Cambridge University Press

Table 1. Demographic and socio-familial characteristics by group[a]

Characteristic	Singletons $n = 144$	First-born twins $n = 37$	Second-born twins $n = 40$
Adjusted age (months)[b]	60.96 ± 8.37	59.77 ± 9.20	58.78 ± 9.55
Gender (F:M)[c]	57:87 [39.58: 60.42%]	16:21 [43.24: 56.76%]	20:20 [50: 50%]
Race (W:O)[d] #	116:28 [80.66: 19.44%]	34:3 [91.89: 8.11 %]	37:3 [92.50: 7.50%]
SES[e]** **	47.73 ± 12.73	53.18 ± 8.11	53.28 ± 12.70
Parental VIQ[f]	105.87 ± 14.19 (128)	108.48 ± 11.06 (33)	107.91 ± 10.01 (34)
Mother's education (yr)	15.41 ± 2.42 (143)	16.05 ± 2.26	16.02 ± 2.17
Father's education (yr)	15.18 ± 2.86 (140)	15.97 ± 2.36	15.92 ± 2.39

Note. Frequencies are reported for discrete data, means and standard deviations for continuous data. Group differences examined *via* t test (continuous data) and 2 × 2 χ^2 with Yates correction (discrete data), or Fisher exact probability test (< five cases per cell). In the case of missing data, number of subjects used is provided in parentheses. Ranges and percentages by group are provided in brackets.

[a]All comparisons between preterm born singletons and twins.

[b]Age at first testing session adjusted for prematurity.

[c]M = male, F = female.

[d]W = White, O = Other (at least one parent not Caucasian). Singletons group included 10 African Americans, 1 Asian, and 17 cases of mixed racial origin (1 African-American/Caucasian, 2 Asian/African Americans, 1 American Indian/Caucasian; 8 Hispanic/Caucasian; 5 Asian/Caucasian). First-, or second-born twin groups each included 2 African American and 1 biracial case (Hispanic-Caucasian).

[e]Hollingshead's (1975) Four Factor Index of Social Status.

[f]Prorated parental IQ based on three subtests (Vocabulary, Similarities, and Information) of the Wechsler Adult Intelligence Scale-III (Wechsler, 1997); Testing was completed on the biological mothers in all cases except 12 singletons and 5 twins, where the father was tested instead.

* $p < .05$, ** $p < .01$, *** $p < .001$ for comparisons of singleton *versus* first-born twin group; $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$ for comparisons of singleton *versus* second-born twin group.

Table 2. Antenatal, perinatal, and neonatal risk by group[a]

Characteristics	Singletons $n = 144$	First-born twins $n = 37$	Second-born twins $n = 40$
Antenatal			
Abruption of the placenta	16 (139) [11.51%]	1 [2.70%]	2 [5.00%]
Chorioamnionitis (histological)	34 [23.61%]	4 [10.81%]	4 [10.00%]
Diabetes[b]	10 [6.94%]	4 [10.81%]	5 [12.50%]
HELLP syndrome[c]	8 (143) [5.59%]	0 [0.00%]	0 [0.00%]
Hypertension in pregnancy*** ***	57 (143) [39.86%]	4 [10.81%]	3 [7.50%]
Intrauterine growth (*Z*-score)[d]	−.130 ± .966	−.098 ± .770	−.114 ± .765
IUGR (<10th centile)	18 [12.5%]	2 [5.40%]	4 [10.00%]
Membranes ruptured (hr)[e] *	44.11 ± 121.00	27.80 ± 93.81	1.20 ± 2.54
Membranes ruptured > 12 hr***	34 [23.61%]	6 [16.22%]	0 [0.00%]
Mother's age at delivery (yr)#	31.48 ± 4.69	33.00 ± 5.05	32.80 ± 4.94
Oligohydramnios#	2 [1.39%]	3 [8.11%]	2 [5.00%]
Parity	.42 ± .78	.62 ± .98	.50 ± .88
Preeclampsia** **	45 (143) [31.47%]	3 [8.11%]	3 [7.50%]
Smoking during pregnancy[f]	20 (140) [14.28%]	4 [10.81%]	3 [7.50%]
Vaginal bleeding (abnormal)*** ***	58 (142) [40.84%]	4 [10.81%]	5 [12.50%]
Total antenatal complications[g] *** ***	1.59 ± 1.04 (140)	.73 ± .80	.70 ± .85
Perinatal			
Abnormal presentation[h] **	45 (143) [31.47%]	12 [32.43%]	21 [52.50%]
Birth weight (g)	1436 ± 555	1432 ± 514	1430 ± 452
Cesarean section# *	79 [54.86%]	27 [72.97%]	30 [75.00%]
Forceps	6 [4.17%]	0 [0.00%]	0 [0.00%]
General anesthesia	12 [8.33%]	1 [2.70%]	1 [2.50%]
Gestational age (wk)[i]	30.08 ± 2.83	30.13 ± 2.65	30.20 ± 2.60
Nuchal cord	24 (142)[16.90%]	6 [16.22%]	5 [12.50%]
Fetal Tachycardia	55 (136) [40.44%]	11 [29.73%]	10 [25.00%]
1 minute Apgar	6.30 ± 1.85	6.43 ± 1.69	6.27 ± 1.75
5 minute Apgar	8.18 ± .94	8.43 ± .76	8.17 ± 1.24
Total perinatal complications[j]	1.476 ± .999 (143)	1.514 ± .932	1.650 ± 1.00
Neonatal			
Anemia at birth[k] # *	20 [13.89%]	1 [2.70%]	1 [2.50%]
Apnea	107 [74.30%]	27 [72.97%]	32 [80.00%]
Bronchopulmonary dysplasia[l]	49 [34.02%]	12 [32.43%]	11 [27.50%]
Days in neonatal intensive care	51.41 ± 42.13	50.54 ± 33.85	47.50 ± 29.43
Hyaline membrane disease[m]	95 [65.97%]	28 [75.67%]	32 [80.00%]
Hyperbilirubinemia[n]	32 [22.22%]	8 [21.62%]	13 [32.50]

https://doi.org/10.1017/S1355617716000758 Published online by Cambridge University Press

Table 2: (*Continued*)

Characteristics	Singletons $n = 144$	First-born twins $n = 37$	Second-born twins $n = 40$
Hypermagnesemia	14 [9.72%]	2 [5.40%]	1 [2.50%]
Hypotension[o]	4 [2.78%]	0 [0.00%]	1 [2.50%]
Intraventricular hemorrhage[p]	21 [14.58%]	9 [24.32%]	4 [10.00%]
Meconium staining/aspiration	4 [2.78%]	0 [0.00%]	0 [0.00%]
Necrotizing enterocolitis[q]	5 [3.47%]	0 [0.00%]	1 [2.50%]
Patent ductus arteriosus[r]	50 [34.72%]	17 [45.94%]	18 [45.00%]
Peak bilirubin (mg/dL)	9.83 ± 2.80	9.55 ± 2.70	9.92 ± 2.53
Persistent pulmonary stenosis	6 [4.17%]	1 [2.70%]	0 [0.00%]
Pneumothorax	6 [4.17%]	2 [5.40%]	2 [5.00 %]
Retinopathy of prematurity[s]	28 [19.44%]	6 [16.22%]	7 [17.50%]
Sepsis (initial or acquired)[t]	21 [14.58%]	7 [18.92%]	4 [10.00%]
Thrombocytopenia	14 [9.72%]	1 [2.70%]	2 [5.00%]
Total neonatal complications[u]	3.16 ± 2.23	3.11 ± 1.93	3.07 ± 1.67
Total complications * *	6.50 ± 2.73 (140)	5.51 ± 2.56	5.42 ± 2.55

Note. Frequencies are reported for discrete data, means and standard deviations for continuous data. Group differences examined *via* t test (continuous data) and 2×2 χ^2 with Yates correction (discrete data), or Fisher exact probability test (<5 cases per cell). In the case of missing data, number of subjects used is provided in parentheses. Ranges and percentages by group are provided in brackets.
[a]All comparisons between preterm-born singleton and twins.
[b]Includes both gestational diabetes and diabetes mellitus.
[c]Hemolysis, elevated liver enzymes and low platelets.
[d]A *Z*-score expressing the deviation of an infant's birth weight from the mean weight of his/her gestational age group, at delivery, in accord with norms published by Kramer et al. (2001).
[e]Time from spontaneous or artificial rupture of membranes to delivery.
[f]Information was available about the mother's smoking behavior during pregnancy for sixteen singleton and five twin cases. For singletons, the mother reported smoking a pack per day in four cases, 11–15 cigarettes per day in three cases, half a pack in three cases, and 1–9 cigarettes per day in six cases. For members of twinships, one mother reported smoking a pack per day and another mother smoked 1–9 cigarettes per day. An additional mother (first-born twin group) smoked half a pack per day.
[g]Total antenatal complications includes placental abruption, histological chorioamnionitis, maternal diabetes, HELLP syndrome, maternal hypertension, IUGR, membranes ruptured >12 hours, multiplicity, and smoking during pregnancy.
[h]Includes various atypical presentations such as breech, transverse lie, footling, etc.
[i]As determined by obstetrician; >95% of cases were corroborated by antenatal ultrasound.
[j]Total perinatal complications include abnormal presentation, C- section, forceps, general anesthesia, nuchal cord, and fetal tachycardia.
[k]Hematocrit < 40%.
[l]BPD was graded as Mild/Moderate for 22 singletons and seven twins, and Severe for 27 singletons and sixteen twins.
[m]Based on a chest roentgenogram and clinical evaluation.
[n]Peak bilirubin ≥ 12 mg/dl.
[o]Requiring treatment.
[p]Documented on the basis of cranial ultrasound. There were 16 cases with Grade I and 5 cases with Grade II in the singletons group. All 13 twin cases were diagnosed with Grade I.
[q]Documented by radiographic changes, positive stool guaiacs, and abdominal distention.
[r]Diagnosed by clinical manifestations and echocardiographic information.
[s]Retinopathy was graded as Stage I for 5 singletons , Stage II for 10 singletons and 8 twins, Stage III for 2 singletons, Stage 3 + for 10 singletons and 3 twins, and Stage IV for one singleton and one twin.
[t]Established by positive blood culture.
[u]Total neonatal complications includes anemia, apnea, hyaline membrane disease, bronchopulmonary dysplasia, hyperbilirubinemia, hypermagnesemia, hypotension, intraventricular hemorrhage, meconium staining/aspiration, necrotizing enterocolitis, patent ductus arteriosus, persistent pulmonary stenosis, pneumothorax, retinopathy of prematurity, sepsis, and thrombocytopenia.
**p* < .05, ***p* < .01, ****p* < .001, # *p* < .10 for comparisons of singleton *versus* first-born twin group; $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$, $^{\#}p < .10$ for comparisons of singleton *versus* second-born twin group.

singleton group, compared to either the first-, or second-born twin groups. Similar to other reports (e.g., Mizrahi et al., 1999), these group differences were primarily attributed to a greater number of antenatal complications in singletons, particularly maternal hypertension, membranes ruptured >12 hr, and abnormal vaginal bleed. Inspection of Table 2 also reveals that abnormal presentation at birth was more common in singletons, yet twins were more likely to be born *via* Cesarean delivery.

Nonetheless, no significant differences were observed in the total number of perinatal complications between singletons and twins. Similarly, although the singletons group was more likely to present with anemia at birth, no significant group differences were observed in the total number of neonatal complications. Table 3 reveals that fertility treatments were characteristic of twin conception, whereas mothers of singletons were more likely to require antepartum magnesium sulfate.

Multiple regression analyses results, using early medical risk and sociodemographic covariates, are reported in Table 4 for the comparison between the singleton and reduced twin group (following random exclusion of a co-twin from the 34 twin pairs comprising our group of 77 twins). Because the predicted Sex by Multiplicity interactions were not significant for either

https://doi.org/10.1017/S1355617716000758 Published online by Cambridge University Press

Table 3. Antenatal and neonatal diagnostic and intervention procedures[a]

Diagnostic and intervention procedures	Singleton $n = 144$	First-born twins $n = 37$	Second-born twins $n = 40$
Antenatal magnesium sulfate[b] * #	88 (141) [62.41%]	16 [43.24%]	19 [47.50 %]
Antenatal steroids[c]	122 (141) [85.82%]	32 [86.49%]	36 [90.00%]
Antenatal steroids dose	2.01 ± 1.89	1.95 ± 2.00	2.30 ± 2.48
Fertility treatment*** ***	6 (142) [4.23%]	10 [27.03%]	13 [32.50%]
Home on apnea monitor	19 [13.19%]	4 [10.81%]	5 [12.50%]
Home on O_2	17 [11.80%]	5 [13.51%]	6 [15.00%]
Neonatal cranial ultrasound	131 [90.97%]	37 [100%]	38 [95.00%]
Neonatal steroids	22 [15.28%]	4 [10.81%]	2 [5.00%]
Surfactant therapy	61 [42.36%]	17 [45.94%]	18 [45.00%]
Total respiratory support days[d]	31.63 ± 47.33	29.03 ± 40.54	25.12 ± 36.25
Ventilation days	11.23 ± 22.20	11.43 ± 23.89	8.68 ± 16.94

Note. Frequencies are reported for discrete data, means and standard deviations for continuous data. Group differences examined *via* t test (continuous data) and 2×2 χ^2 with Yates correction (discrete data), or Fisher exact probability test (<5 cases per cell). In the case of missing data, number of subjects used is provided in parentheses. Ranges and percentages by group are provided in brackets.
[a]All comparisons between preterm-born singletons and twins.
[b]Magnesium sulfate, administered to inhibit preterm labor and/or control seizures in preeclampsia.
[c]Betamethasone, to promote fetal lung maturation.
[d]Including mechanical ventilation, continuous positive airway pressure (CPAP), nasal cannulae, and oxyhood.
*$p < .05$, ***$p < .001$ for comparisons of singleton *versus* first-born twin group; ***$p < .001$, # $p < .10$ for comparisons of singleton *versus* second-born twin group.

memory ($F[1,170] = .028$; $p = .868$), language ($F[1,174] = .157$; $p = .693$), or motor ($F[1,172] = .003$; $p = .958$) performance, we used the reduced models. Twin boys tended to score lower on the visual processing task, yet the Sex by Multiplicity interaction did not attain statistical significance ($F[1,170] = 3.527$; $p < .062$).

Examination of the relationships between the predictor of interest and the three global scaled scores presented in Table 4 (LTR, TL, and TM) reveals that multiplicity was significantly associated only with global language performance ($p = .029$). The adjusted means $\pm$ *SE* for TL were 97.44 ± 2.34 *versus* 102.89 ± 1.31 for the twin and singleton groups, respectively (Cohen's $d = .33$; see Figure 1), falling well within the Average range. Follow-up univariate analyses disclosed that the relationships between multiplicity and either AC ($p = .072$) or EC ($p = .043$) scores did not attain statistical significance following Bonferroni correction ($\alpha = .025$). The results presented in the table also reveal that, among the perinatal predictors, intrauterine growth (*Z*-score) was associated with TL performance ($p = .038$), while the total complications summary score was inversely related to TM performance ($p = .002$).

Analyses of visual processing skills reveal a significant association between multiplicity and the PC subtest scores ($p = .03$; Table 4). The adjusted means $\pm$ *SE* were 97.92 ± 2.28 *versus* 103.69 ± 1.26 (Cohen's $d = .38$; see Figure 2) for the twin and singleton groups, respectively, falling well within the Average range. None of the predictors indexing perinatal risk accounted for a significant portion of the variance in visual processing skills.

Supplemental analyses revealed that addition of fertility treatment as a predictor in our regression model yielded no associations between use of assisted reproductive technology and either TL ($F[1,173] = .009$; $p = .926$) or PR ($F[1,169] = .045$; $p = .833$) scores. Additionally, a comparison between monochorionic and dichorionic twins in the reduced twin group yielded no significant differences ($t[37] = -.352$; $p = .543$ and $t[36] = -.658$; $p = .515$ for TL and PC scores, respectively).

Tables 5 and 6 provide results from comparisons of outcome measures between first-, or second-born twins and singletons, respectively. As shown in these tables, comparisons of overall language performance of either first-, or second-born twins with their singleton counterparts yielded similar findings to those reported for comparisons of singletons with the reduced twin group (Table 4). Multiplicity accounted for TL scores regardless of birth-order ($p = .036$ and $p = .029$ for first-, and second-born twins, respectively). In contrast with the findings obtained for the reduced twin group, the differences in visual processing skills between first (Table 5) or second-born (Table 6) twins and their singleton counterparts did not attain statistical significance ($p = .109$ and $p = .175$, respectively).

Supplemental comparisons were conducted between singletons, and either the 34 first-, or second-born co-twins, following exclusion of the nine twins whose co-twin could not be included in our study. Similar to the results presented in Tables 5 and 6, multiplicity accounted for TL performance regardless of birth order ($F[1,66] = 4.60$; $p = .033$, with adjusted means $\pm$ $SE = 96.71 \pm 2.64$ *vs.* 103.05 ± 1.28, for first born twins *vs.* singletons, respectively [Cohen's $d = .40$] and F [1, 66] = 8.80; $p = .003$ with adjusted means $\pm$ $SE = 94.22 \pm 2.63$ *vs.* 102.96 ± 1.28, for second-born twins *vs.* singletons, respectively [Cohen's $d = .56$]). However, with α adjustment (.025), only the second-, but not first-born,

https://doi.org/10.1017/S1355617716000758 Published online by Cambridge University Press

Table 4. Multiple regression analyses: reduced twin *versus* singleton group

		Domain scores			Subscale/subtest score[1]					
Memory & Learning	Variables	*F*(LTR) *df* = 1,168[a]	*p*	η^2P	*F*(VAL) *df* = 1,172	*p*	η^2P	*F*(RFL) *df* = 1,168[b]	*p*	η^2P
	SES	11.440	.001	.0641	10.535	.001	.0577	19.682	.000	.1049
	Sex	7.807	.006	.0437	1.166	.282		14.051	.000	.0772
	Birth weight	.396	.530		.790	.375		3.321	.070	
	Growth *Z*-score	.034	.855		.112	.738		1.364	.245	
	Complications	1.072	.302		2.788	.097		.541	.463	
	Multiplicity	.563	.454		.416	.520		1.268	.262	
Language	Variables	*F*(TL) *df* = 1,175[c]	*p*	η^2P	*F*(AC) *df* = 1,175[c]	*p*	η^2P	*F*(EC) *df* = 1,176	*p*	η^2P
	SES	13.239	.000	.0703	9.476	.002	.0514	11.373	.001	.0607
	Sex	3.946	.049	.0220	5.476	.020		2.920	.089	
	Birth weight	.351	.554		.001	.970		.340	.560	
	Growth *Z*-score	4.384	.038	.0244	3.255	.073		2.554	.112	
	Complications	1.315	.253		.007	.932		4.153	.127	
	Multiplicity	4.876	.029	.0271	3.280	.072		3.716	.043	
Visual Processing	Variables				*F*(PR) *df* = 1,171	*p*	η^2P			
	SES				14.529	.000	.0783			
	Sex				.409	.523				
	Birth weight				.018	.892				
	Growth *Z*-score				1.769	.185				
	Complications				.950	.331				
	Multiplicity				4.813	.030	.0274			
Motor	Variables	*F*(TM) *df* = 1,172[d]	*p*	η^2P	*F*(FM) *df* = 1,173	*p*	η^2P	*F*(GM) *df* = 1, 172[d]	*p*	η^2P
	SES	7.640	.006	.0425	6.450	.012	.0355	3.821	.052	
	Sex	3.665	.057	.0209	5.612	.019	.0311	1.319	.252	
	Birth weight	0.135	.714		.131	.718		.239	.626	
	Growth *Z*-score	1.529	.218		.788	.093		2.134	.146	
	Complications	9.569	.002	.0527	2.846	.170		10.971	.001	.0599
	Multiplicity	2.396	.123		1.899	.159		1.352	.247	

Note. Memory indices include the Woodcock Johnson - III Tests of Cognitive Abilities (Woodcock, McGrew, & Mather, 2001) Long Term Retrieval (LTR) cluster score, the Visual Auditory Learning (VAL) and Retrieval Fluency (RFL) subtest scores; language indices include the Preschool Language Scale III (Zimmerman, Steiner & Pond, 1992) Total Language (TL), Auditory Comprehension (AC) and Expressive Communication (EC); visual processing include the WJ-III Tests of Cognitive Abilities Picture Recognition (PR)subtest; motor indices include the Peabody Developmental Motor Scales II (Folio & Fewell, 2000) Fine Motor quotient (FM) and Gross Motor quotient (GM).
[a]Four multivariate outliers (three with studentized residuals < −3.3 and one with residual = 3.66) were removed.
[b]Two multivariate outliers (studentized residuals < −3.64) were removed.
[c]A multivariate outlier (studentized residual = −3.78) was removed.
[d]A multivariate outlier (studentized residual = −5.15) was removed.
[1]Bonferroni-corrected α levels (.025) were used to determine statistical significance of associations between predictors and subscale or subtest performance, with familywise adjustments within outcome domains.

twins differed from singletons in global language outcome (TL scores). Additional comparisons of PR subtest scores between 136 singletons and either 31 first-born, or their second-born, co-twins who completed this subtest yielded similar findings to those reported in Table 5 ($F[1,160] = 2.42$; $p = .12$) and Table 6 ($F[1,160] = 3.44$; $p = .066$), respectively.

Among sociodemographic covariates, SES was significantly associated with performance in all four outcome domains (Tables 4–6) with the single exception of a trend for an association with GM performance in second-born twins ($p < .056$; Table 6). Significant associations were also observed between sex and both global memory and language performance (all p levels < .05; Tables 4–6), with girls outperforming boys.

DISCUSSION

We compared the neuropsychological functioning of preterm twins and singletons at preschool age on memory, language,

https://doi.org/10.1017/S1355617716000758 Published online by Cambridge University Press

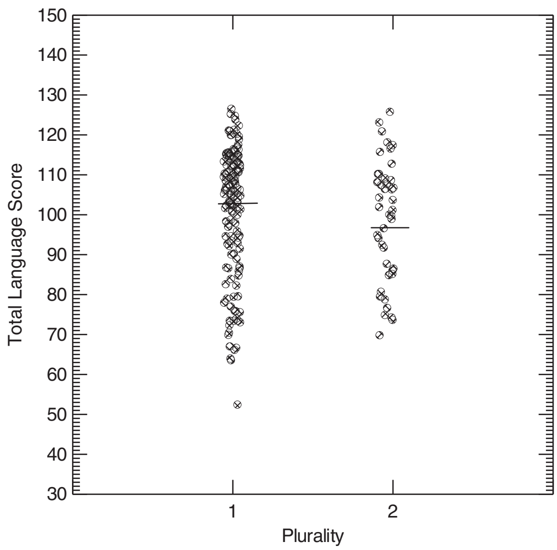

Fig. 1. Total Language scores by group. Plurality: 1 = singletons (n = 144) and 2 = reduced twin group (n = 43). The adjusted means ± *SE* for Total Language score were 97.44 ± 2.34 *versus* 102.89 ± 1.31 for the twin and singleton groups, respectively (Cohen's d = .33). Slight random jitter applied to disperse overlapping observations.

visual processing, and motor tasks. In addition to socioeconomic advantage, the twin group was characterized by reduced early medical risk compared to singletons. An increase in the frequency of various maternal complications in singletons, compared to twins, has also been observed in population studies of very preterm cohorts (e.g., Bodeau-livinec et al., 2013; Papiernik et al., 2010). If anything, higher familial SES coupled with reduced medical risk in our multiples may have only served to dilute the group differences observed here.

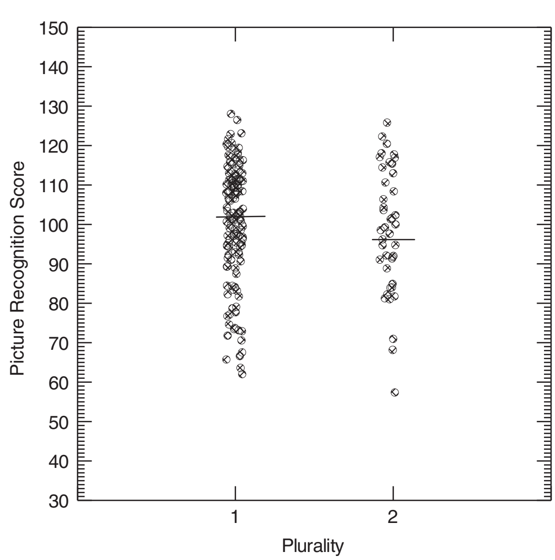

Fig. 2. Picture Recognition subtest scores by group. Plurality: 1 = singleton group (n = 144) and 2 = reduced twin group (n = 43). The adjusted means ± *SE* for Picture Recognition score were 97.92 ± 2.28 *versus* 103.69 ± 1.26 (Cohen's d = .38) for the twin and singleton groups, respectively (Cohen's d = .33). Slight random jitter applied to disperse random observations.

Nonetheless, neuropsychological assessment at preschool age revealed that, despite reduced social and biological risk, the twin group did not fare better in comparison to their singleton counterparts. Overall language performance was found to be significantly poorer in twins, with group differences of .33 *SD*s. Twins also exhibited reduced visual-spatial skills, with group differences of .38 *SD*s. In contrast with sporadic reports in the twin development literature (Gucuyener et al., 2011; Thorpe, 2006), we found little evidence of a male-twin disadvantage either for language or other outcome domains, as indicated by the absence of significant Multiplicity by Sex interaction effects.

Notwithstanding the increase in the proportion of twins within the population of premature infants, few surfactant-era studies have been dedicated to the examination of the unique contribution of multiplicity to neuropsychological functioning at preschool or school age. Einaudi et al. (2008) were unable to demonstrate differences between 23 twins and 31 singletons, born <32 weeks gestation, in the frequency of either "comprehensive retardation" or language delay. In contrast, Bodeau-Livinec and the EPIPAGE group (2013) were able to show a small difference of 2.4 points on the Mental Processing Composite (Kaufman Assessment Battery for Children, 1983), in favor of singletons, following adjustment for socioeconomic and early medical risk.

Our findings of mild language and visual processing deficits in preterm-born twins are consistent with the results reported by the EPIPAGE group. Of interest, second- but not first-born twins' total language scores significantly differed from those of singletons in our supplemental analyses of the 34 pairs of twins. However, group differences approximated or equaled a moderate effect size in both comparisons (Cohen's d = .56 and .40, respectively) and the relatively small number of cases per group constrained our ability to establish a birth-order effect.

A group of environmental conditions that may explain differences in language development between singletons and twins are twinning-specific phenomena (e.g., TTTS or private language; Thorpe, 2006). While the "private language" explanation cannot be completely discounted based on our findings, the co-existing relative deficit in visual processing skills, observed in the reduced twin group, mitigates against "private language" explanations of the mild to moderate (Cohen's d = .33–.56) language gaps documented here. An adverse early biological factor specific to twinning could also not be easily negated by our findings. TTTS of different grades of severity (Rychik et al., 2007) and several other unique complications, also attributed to presence of placental vascular anastomoses, are phenomena occurring in complicated monochorionic twin pregnancies (Moldenhauer & Johnson, 2015).

Our analyses revealed that the differences observed in language skills were likely not linked to type of placentation in our twin group, nor were they attributable to the three cases with

https://doi.org/10.1017/S1355617716000758 Published online by Cambridge University Press

Table 5. Multiple regression analyses: first-born twin *versus* singleton group

		Domain scores			Subscale/subtest scores[1]					
Memory & Learning	Variables	F(LTR) $df = 1{,}163^a$	p	η^2P	F(VAL) $df = 1{,}166$	p	η^2P	F (RFL) $df = 1{,}164$	p	η^2P
	SES	17.886	.000	.0989	10.213	.002	.0579	34.067	.000	.1720
	Sex	6.842	.010	.0403	.998	.319		11.184	.001	.0638
	Birth weight	.720	.397		.679	.411		4.164	.043	
	Growth *Z*-score	.679	.411		.184	.669		0.009	.924	
	Complications	5.584	.019	.0331	3.752	.054		7.803	.006	.0454
	Multiplicity	1.372	.243		.847	.359		1.647	.201	
Language	Variables	F (TL) $df = 1{,}169^b$	p	η^2P	F (AC) $df = 1{,}169^b$	p	η^2P	F (EC) $df = 1{,}170$	p	η^2P
	SES	15.163	.000	.0823	11.173	.001	.0661	12.801	.000	.0700
	Sex	5.316	.022	.0305	6.750	.010	.0384	4.302	.040	
	Birth Weight	0.017	.896		0.374	.542		0.028	.868	
	Growth *Z*-score	2.206	.139		1.365	.244		1.216	.272	
	Complications	0.689	.408		0.050	.823		0.705	.402	
	Multiplicity	4.473	.036	.0258	1.583	.210		5.452	.021	0311
Visual Processing	Variables				F (PR) $df = 1{,}165$	p	η^2P			
	SES				10.743	.001	.0651			
	Sex				.113	.738				
	Birth Weight				.651	.421				
	Growth *Z*-score				.959	.329				
	Complications				.836	.362				
	Multiplicity				2.590	.109				
Motor	Variables	F (TM) $df = 1{,}167^c$	p	η^2P	F (FM) $df = 1{,}169$	p	η^2P	F (GM) $df = 1{,}167^c$	p	η^2P
	SES	8.820	.003	.0502	6.531	.011	.0372	5.099	.025	.0296
	Sex	3.013	.084		5.641	.019		.543	.462	
	Birth Weight	.664	.416		.232	.631		1.152	.285	
	Growth *Z*-score	1.076	.301		.554	.458		1.531	.218	
	Complications	8.236	.005	.0470	3.229	.074		8.047	.005	.0460
	Multiplicity	1.616	.205		.496	.482		1.651	.201	

Note. Memory indices include the Woodcock Johnson - III Tests of Cognitive Abilities (Woodcock, McGrew, & Mather, 2001). Long Term Retrieval (LTR) cluster score, the Visual Auditory Learning (VAL), and Retrieval Fluency (RFL) subtest scores; language indices include the Preschool Language Scale III (Zimmerman, Steiner & Pond, 1992) Total Language (TL), Auditory Comprehension (AC) and Expressive Communication (EC); visual processing include the WJ-III Tests of Cognitive Abilities Picture Recognition (PR) subtest; motor indices include the Peabody Developmental Motor Scales II (Folio & Fewell, 2000) Fine Motor quotient (FM) and Gross Motor quotient (GM).
[a]Two multivariate outliers with (studentized residuals = −3.63 and 3.81) were removed.
[b]A single multivariate outlier (studentized residual = −3.91) was removed.
[c]A single multivariate outlier (studentized residual = −5.23) was removed.
[1]Bonferroni-corrected α levels (.025) were used to determine statistical significance of associations between predictors and subscale or subtest performance, with familywise adjustments within outcome domains.

TTTS whose language scores fell well within or above the average range. We should note here that the current investigation was not designed to evaluate outcome effects of placentation or fertility treatment, as only ten (23.6%) monochorionic and thirteen (30.23%) ART cases were available for study in the reduced twin group.

Another group of conditions that may account for performance deficits in twins are adverse pre- and perinatal events not specific to twinning. In the current study, we documented a multitude of discrete perinatal complications and attempted to account for early biological risk. Indeed, the sum of pre-, peri-, and neonatal complications explained a significant portion of the variance in motor performance, while adequacy of intrauterine growth accounted for variance in language skills (Table 4). Nonetheless, multiplicity explained a unique portion of variance in language and visual

https://doi.org/10.1017/S1355617716000758 Published online by Cambridge University Press

Table 6. Multiple regression analyses: second-born twin *versus* singleton group

		Domain scores			Subscale/subtest score[1]					
Memory & Learning	Variables	F(LTR) $df = 1{,}162$[a]	p	η^2P	F(VAL) $df = 1{,}167$	p	η^2P	F (RFL) $df = 1{,}163$[b]	p	η^2P
	SES	12.071	.001	.0693	11.986	.001	.0670	17.598	.000	.0974
	Sex	6.475	.012	.0384	1.092	.298		10.541	.001	.0607
	Birth weight	.676	.412		.298	.586		2.465	.118	
	Growth *Z*-score	.037	.849		.285	.594		2.658	.105	
	Complications	1.031	.311		3.476	.064		0.108	.743	
	Multiplicity	.099	.754		.496	.482		.019	.890	
Language	Variables	F (TL) $df = 1{,}172$[c]	p	η^2P	F (AC) $df = 1{,}172$[c]	p	η^2P	F (EC) $df = 1{,}173$	p	η^2P
	SES	12.443	.001	.0674	8.233	.005	.0457	11.382	.001	.0617
	Sex	4.133	.044	.0235	5.829	.017	.0328	2.942	.088	
	Birth weight	.157	.693		.035	.852		.157	.692	
	Growth *Z*-score	2.593	.109		2.699	.102		.820	.366	
	Complications	.881	.349		.027	.870		2.016	.157	
	Multiplicity	4.877	.029	.0275	3.810	.053		3.716	.056	
Visual Processing	Variables				F (PC) $df = 1{,}166$	p	η^2P			
	SES				12.980	.000	.0725			
	Sex				.046	.831				
	Birth weight				.176	.675				
	Growth *Z*-score				1.411	.237				
	Complications				.058	.810				
	Multiplicity				1.859	.175				
Motor	Variables	F (TM) $df = 1{,}168$[d]	p	η^2P	F (FM) $df = 1{,}171$	p	η^2P	F (GM) $df = 1{,}168$[d]	p	η^2P
	SES	6.882	.010	.0393	5.704	.018	.0322	3.718	.056	
	Sex	3.058	.082		4.810	.030	.0273	1.105	.295	
	Birth weight	0.065	.799		.007	.931		.611	.436	
	Growth *Z*-score	1.104	.295		.850	.358		1.187	.277	
	Complications	8.753	.004	.0495	2.883	.091		9.676	.002	.0544
	Multiplicity	.924	.338		1.406	.237		.174	.677	

Note. Memory indices include the Woodcock Johnson - III Tests of Cognitive Abilities (Woodcock, McGrew, & Mather, 2001), Long Term Retrieval (LTR) cluster score, the Visual Auditory Learning (VAL) and Retrieval Fluency (RFL) subtest scores; language indices include the Preschool Language Scale III (Zimmerman, Steiner & Pond, 1992) Total Language (TL), Auditory Comprehension (AC) and Expressive Communication (EC); visual processing include the WJ-III Tests of Cognitive Abilities Picture Recognition (PR) subtest; motor indices include the Peabody Developmental Motor Scales II (Folio & Fewell, 2000), Fine Motor quotient (FM), and Gross Motor quotient (GM).
[a]Two multivariate outliers (three with studentized residuals < -3.64 and one with residual of 3.68) were removed.
[b]Two multivariate outliers (studentized residuals < -3.64) were removed.
[c]A multivariate outlier (studentized residual $= -3.78$) was removed.
[d]A multivariate outlier (studentized residual $= -5.14$) was removed.
[1]Bonferroni-corrected α levels (.025) were used to determine statistical significance of associations between predictors and subscale or subtest performance, with familywise adjustments within outcome domains.

processing skills, over and above the variance associated with early medical risk.

Despite our efforts, we cannot exclude the possibility that an undocumented early biological risk factor, whether unique to twinning or simply more common in twins, accounts for the statistically significant, albeit relatively modest, language and visual processing skill disadvantage observed in twins. Indeed, detection of an early biological risk factor explaining the language gap observed here would be consistent with the claim that the perinatal environment (which is overwhelmingly biological) affects linguistic development more than the postnatal environment (which is preponderantly psychosocial; Stromwold, 2006).

Our findings should be viewed as applicable primarily to middle class families, as generalizability to lower strata was

https://doi.org/10.1017/S1355617716000758 Published online by Cambridge University Press

traded-off for higher internal validity. Lower SES is typically associated with reduced access to prenatal care, fewer socio-educational or therapeutic opportunities during infancy and the preschool years, and increased exposure to a variety of environmental insults. Adverse circumstances, in turn, may increase the heterogeneity of the sample and introduce variance that may confound or dilute the effects of multiple birth and perinatal complications on neuropsychological functioning.

Our perinatal data were collected retrospectively, and our investigation was cross-sectional, with participants' average age of approximately 5 years. It is yet to be determined whether the findings are generalizable to younger preschoolers or to the elementary school years and beyond. A longitudinal investigation will facilitate exploration of age-related effects of multiplicity on neuropsychological outcome domains in children born prematurely. In accord with a recent report of age-related decline in language performance in preterm children (Stolt et al., 2014), it is possible that multiplicity contributes a share to these phenomena. For instance, multiplicity may "exert" negligible developmental outcome effects in infancy that evolve into modest to moderate effects in late preschool age and larger effects in the primary and middle school years.

To conclude, the findings from this investigation suggest that preterm-born twins are at somewhat higher risk for language and visuospatial skill deficits at preschool age compared to their singleton counterparts, possibly a result of biological factors. Early detection, accompanied by interventions such as language therapy and reinforcement of preacademic skills, is essential for preterm-born multiples, yet will likely benefit both at-risk groups. In addition to investigating age-related effects, neuropsychological functions other than those examined in the current study (e.g., executive) should be studied in preterm twins and singletons, as they may prove to be more sensitive to adverse effects of twinning.

ACKNOWLEDGMENTS

The authors thank Elizabeth Kring, Tammy Swails, Amanda Shoemaker, Jacquie Perry, and Sarah Meachen for their help in data collection. The study was funded in part by the Merrill-Palmer Skillman Institute. None of the authors has a known conflict of interest concerning this manuscript.

REFERENCES

Arnold, C., McLean, F.H., Kramer, M.S., & Usher, R.H. (1987). Respiratory distress syndrome In second-born versus first-born twins. A matched case-control analysis. *New England Journal of Medicine*, *317*, 1121–1125.

Armson, B.A., O'Connell, C., Persad, V., Joseph, K.S., Young, D.C., & Baskett, T.F. (2006). Determinants of perinatal mortality and serious neonatal morbidity in the second twin. *Obstetrics & Gynecology*, *108*, 556–564.

Asztalos, E., Barrett, J.F.R., Lacy, M., & Luther, M. (2001). Evaluating 2 year outcome in twins ≤ 30 weeks gestational at birth: A regional perinatal unit's experience. *Twin Research*, *4*, 431–438.

Batton, D.G., DeWitte, D.B., & Pryce, C.J. (2011). One hundred consecutive infants born at 23 weeks and resuscitated. *American Journal of Perinatology*, *28*, 299–304. doi:10.1055/s-0030-1268714

Bodeau-Livinec, F., Zeitlin, J., Blondel, B., Arnaud, C., Fresson, J., & Burguet, A., . . . the EPIPAGE group. (2013). Do very preterm twins and singletons differ in their neurodevelopment at 5 years of age? *Archives of Disease in Childhood: Fetal Neonatal Edition*, *98*, F480–F487. doi:10.1136/archdischild-2013-303737

Einaudi, M.A., Busuttil, M., Monnier, A.-S., Chanus, I., Palix, C., & Gire, C. (2008). Neuropsychological screening of a group of preterm twins: Comparison with singletons. *Child's Nervous System*, *24*, 225–230. doi:10.1007/s00381-007-0422-6

Eras, Z., Ozyurt, B.M., Kanmaz, G., Erdeve, O., Sakrucu, E.D., Oguz, S.S., … Dilmen, U. (2013). *Twin Research and Human Genetics*, *16*, 614–618. doi:10.1017/thg.2012.155

ESHRE Capri Workshop Group. (2000). Multiple gestation pregnancy. *Human Reproduction*, *15*, 1856–1864.

Gonzalez-Mesa, E., Cazorla-Granados, O., & Gonzalez-Valenzuela, M.J. (2016). The influence of obstetric variables on school achievement, intelligence and neuropsychological development in a sample of Spanish twins at the age of six: A retrospective study. *Journal of Maternal-Fetal & Neonatal Medicine*, *29*(10), 1595–1602.

Gucuyener, K., Arhan, E., Soysal, A.S., Ergenekon, E., Turan, O., Onal, E., … Atalay, Y. (2011). Language assessment of non-handicapped twins at 5 years of age. *Pediatrics International*, *53*, 944–949.

Hacking, D., Watkins, A., Fraser, S., Wolfe, R., & Nolan, T. (2001). Respiratory distress syndrome and birth order in premature twins. *Archives of Disease in Childhood Fetal and Neonatal Edition*, *84*, F117–F121. doi:10.1136/fn.84.2.F117

Hajnal, B.L., Braun-Fahrlander, C., von Siebenthal, K., Bucher, H.U., & Largo, R.H. (2005). Improved outcome for very low birth weight multiple births. *Pediatric Neurology*, *32*, 87–93. doi:10.1016/j.pediatrneurol.2004.09.004

Hollingshead, A.B. (1975). A four factor index of social status. Unpublished working paper. New Haven, CT: Department of Sociology, Yale University.

Jobe, A.H., & Bancalari, E. (2001). Bronchopulmonary dysplasia. *American Journal of Respiratory Critical Care Medicine*, *163*, 1723–1729. doi:10.1164/ajrccm.163.7.2011060

Kaufman, A.S. (1983). *Kaufman Assessment Battery for Children (K-ABC)*. Circles Pines, MN: American Guidance Service.

Kramer, M.S., Platt, R.W., Wen, S.W., Joseph, K.S., Allen, A., Abrahamowicz, M., … Breart, G. (2001). A new and improved population-based Canadian reference for birth weight for gestational age. *Pediatrics*, *108*, E35. doi:10.1542/peds.108.2.e35

Kyriakidou, M., Karagianni, P., & Iliodromiti, Z. (2013). Comparison of 24 months neurodevelopmental outcome in twins and singletons ≤ 34 weeks gestation at birth. *Journal of Pediatric and Neonatal Individualized Medicine (JPNIM)*, *2*, 48–54. doi:10.7363/020101

Lee, S.M., Park, J.S., Norwitz, E.R., Kim, S.M., Lee, J., Park, C.-W., … Jun, J.K. (2015). Presenting twins are exposed to higher levels of inflammatory mediators than nonpresenting twins as early as the midtrimester of pregnancy. *PLoS One*, *10*(6), e0125346. doi:10.1371/journal.pone.0125346

Lorenz, J.M. (2012). Neurodevelopmental outcomes of twins. *Seminars in Perinatology*, *36*, 201–201. doi:10.1053/j.semperi.2012.02.005

Manuck, T.A., Sheng, X., Yoder, B.A., & Varner, M.W. (2014). Correlation between initial neonatal and early childhood outcomes following preterm birth. *American Journal of Obstetrics and Gynecology*, *210*, 426.e1–e9. doi:10.1016/j.ajog.2014.01.046

Martin, J.A., Hamilton, B.E., & Osterman, M.J. (2012). Three decades of twin births in the United States, 1980–2009. *National Center for Health Statistics Data Brief*, *80*, 1–8.

Martin, J.A., Hamilton, B.E., Ventura, S.J., Osterman, M.J.K., Wilson, E.C., & Mathews, T.J. (2012). Births: Final data for 2010. *National Vital Statistics Reports*, *61*, 1–72.

Martin, J.A., Hamilton, B.E., Ventura, S.J., Osterman, M.J.K., & Mathews, T.J. (2013). Births: Final data for 2011. *National Vital Statistical Reports*, *62*, 1–70.

Mizrahi, M., Furman, B., Shoham-Vardi, I., Vardi, H., Maymon, E., & Mazor, M. (1999). *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, *87*, 55–61.

Moldenhauer, J.S., & Johnson, M.P. (2015). Diagnosis and management of complicated monochorionic twins. *Clinical Obstetrics and Gynecology*, *58*, 632–642. doi:10.1097/GRF.0000000000000127

Papiernik, E., Zeitlin, J., Delmas, D., Blondel, B., Kunzel, W., Cuttini, M., … Draper, E.S., MOSAIC Group. (2010). Differences in outcome between twins and singletons born very preterm: results from a population-based European cohort. *Human Reproduction*, *25*, 1035–1043. doi:10.1093/humrep/dep430

Rychik, J., Tian, Z., Bebbington, M., Xu, F., McCann, M., Mann, S., … Johnson (2007). The twin-twin transfusion syndrome: spectrum of cardiovascular abnormality and development of a cardiovascular score to assess severity of disease. *American Journal of Obstetrics and Gynecology*, *197*, 392.e1–8.

Rysavy, M.A., Li, L., Bell, E.F., Das, A., Hintz, S.R., Stoll, B.J., … Higgins, R. (2015). Between hospital variation in treatment and outcomes in extremely preterm infants. *New England Journal of Medicine*, *19*, 1801–1811. doi:10.1056/NEJMoa1410689

Schrank, F.A. (2011). Woodcock-Johnson III tests of cognitive abilities. In A.S. Davis (Ed.), *Handbook of pediatric neuropsychology* (pp. 415–434). New York: Springer Publishing Company.

Smith, L.K., Manktelow, B.N., Draper, E.S., Boyle, E.M., Johnson, S.J., & Field, D.J. (2014). Trends in the incidence and mortality of multiple births by socioeconomic deprivation and maternal age in England: population-based cohort study. *BMJ Open*, *3*(4), e004514. doi:10.1136/bmjopen-2013-004514

Stolt, S., Matomaki, J., Lind, A., Lapinleimu, H., Haataja, L., & Lehtonen, L. (2014). The prevalence and predictive value of weak language skills in children born with very low birth weight – a longitudinal study. *Acta Paediatrica*, *103*, 651–658. DOI:10.1111/apa.12607

Stromwold, K. (2006). Genetic, prenatal and postnatal factors. *Cognition*, *101*, 333–384. doi:10.1016/j.cognition.2006.04.007

Sunderam, S., Kissin, D.M., Crawford, S.B., Folger, S.G., Jamieson, D.J., Warner, L., … Barfield, W.D. (2015). Assisted reproductive technology surveillance-United States, 2012. *Morbidity and Mortality Weekly Report Surveillance Summary*, *64*, 1–29.

Thorpe, K. (2006). Twin children's language development. *Early Human Development*, *82*, 387–395.

Voracek, M., & Haubner, T. (2008). Twin-singleton differences in intelligence: A meta-analysis. *Psychological Reports*, *102*, 951–962. doi:10.2466/pr0.102.3.951-962

Wadhawan, R., Oh, W., Perritt, R.L., McDonald, S.A., Das, A., Poole, W.K., … Higgins, R.D. (2009). Twin gestation and neurodevelopmental outcome in extremely low birth weight infants. *Pediatrics*, *123*, e220–e227. doi:10.1542/peds.2008-1126

Wechsler, D. (1997). *Wechsler Adult Intelligence Scale - 3rd edition*. San Antonio: The Psychological Corporation.

Woodcock, R.W., McGrew, K.S., & Mather, N. (2001). *Woodcock-Johnson Tests of Cognitive Abilities (WJ III)*. Rolling Meadows, IL: Riverside Publishing.

Yeung, E.H., Sundaram, R., Bell, E.M., Druschel, C., Kus, C., Ghassabian, A., … Buck Louis, G.M. (2016). Examining infertility treatment and early childhood development in the Upstate KIDS Study. *Journal of the American Medical Association: JAMA Pediatrics*, *170*, 251–258. doi:10.1001/jamapediatrics.2015.4164

Zimmerman, I. L., Steiner, V. G., & Pond, R. E. (1992). *Preschool Language Scale - 3rd Edition*. San Antonio: The Psychological Corporation.

Zork, N., Biggio, J., Tita, A., Rouse, D., & Gyamfi-Bannerman, C. (2013). Decreasing prematurity in twin gestations: Predicaments and possibilities. *Obstetrics and Gynecology*, *122*, 375–379. doi:10.1097/AOG.0b013e31829b2dba