An Investigation Into Etiological Pathways of DCD and ADHD Using a Monozygotic Twin Design

Jillian G. Pearsall-Jones,[1,2] Jan P. Piek,[1] Daniela Rigoli,[1] Neilson C. Martin,[1] and Florence Levy[3]

[1] School of Psychology, Curtin University of Technology, Australia
[2] The Centre for Cerebral Palsy, Perth, Australia
[3] School of Psychiatry, University of New South Wales, Sydney, Australia

We previously described a co-twin control design using questionnaire data on monozygotic twins discordant and concordant for developmental coordination disorder (DCD) and attention deficit hyperactivity disorder (ADHD). Our results suggested that DCD and developmental ADHD had different causal pathways, and that second-born twins were at higher risk for oxygen perfusion problems than first-born twins. In the current study we further explored our findings using DNA confirmed zygosity and assessments of 4 female and 10 male sets of monozygotic twins, aged 8 to 17 years, from the first study. Using the McCarron Assessment of Neuromuscular Development (MAND), twice as many second- as first-born twins met criteria for DCD. Second-born twins attained significantly lower scores on 1-minute Apgar, MAND Gross Motor, Bimanual Dexterity and Neuromuscular Development Index. Seven of the nine twins who met criteria for DCD experienced perinatal oxygen perfusion problems. This supported findings in the first study of an association between perinatal oxygen perfusion problems and DCD, and our hypothesis that DCD and cerebral palsy have similar causal pathways. We found similar numbers of males and females discordant for DCD. On telephone interview using the Diagnostic Interview Schedule for Children Parent Interview, the only first-, and all five second-born twins who met criteria for ADHD had an inattentive component — three Inattentive; three Combined. All twins positive for ADHD were male. This adds support to our hypothesis that ADHD symptoms found in some participants may reflect secondary ADHD associated with environmental factors, rather than developmental ADHD.

Keywords: monozygotic twin, genetic, discordant, concordant, ADHD, DCD, etiology, oxygen perfusion, environmental

Into the 21st century, behavior genetic twin research has become pivotal in attaining estimates for the relative contribution of genetic and environmental factors to disorders such as Developmental Coordination Disorder (DCD) and Attention Deficit Hyperactivity Disorder (ADHD). However, there is increasing interest in epigenetic processes and other external and internal factors that might lead to different phenotypes in individuals with the same genotype. The co-twin control, or twin-differences design (Martin et al., 1997), with its focus on monozygotic (MZ) twins discordant for wellness and disorder, provides a unique means by which to control for potentially confounding factors such as genotype, gender, age, socioeconomic status, and shared family environment.

Factors leading to discordance in MZ twins include the stage (Race et al., 2006) and equality of splitting of the zygote (Sperber et al., 1994). Monochorionic monoamniotic twins are at high risk for twin-to-twin transfusion syndrome (TTTS), which may result in acute or chronic episodes of hemodynamic instability at various stages during pregnancy, and can cause ischemic damage (Pharoah, 2006). Lifelong discordance for phenotype can also result from different vascular patterns in the placenta of monochorionic MZ twins (Machin et al., 1996).

During the prenatal period, discordance may also result from post zygotic epigenetic effects such as tissue specific patterns of methylation (Bennett et al., 2008); varying patterns of methylation maintenance (Brown & Robinson, 2000); and chromatin remodeling (Wilson, 2008). Fraga and colleagues (2005) found that although in their younger years MZ twins were epigenetically indistinguishable, as they aged epigenetic differences, such as disease susceptibility, became more divergent.

Different exposure or response to toxins and infections may occur in utero (Iwayama et al., 2007) and at birth, sometimes affecting only one twin (Dulière et al., 1995; Forrester et al., 1966). Timing of exposure to infections is important, and may have long-term

cumulative effects; for example, increased sensitization to hypoxia at birth and in later life (Gunn & Bennet, 2008). Discordant outcome may also be a result of birth complications and presentation (Bjelic-Radisic et al., 2007) and birth order (Hartley & Hitti, 2005; Smith et al., 2007).

Developmental coordination disorder (DCD), or specific developmental disorder of motor function, are described respectively in both the *Diagnostic and Statistical Manual of Mental Disorders — Fourth Edition Text Revision* (DSM-IV-TR — American Psychiatric Association (APA), 2000) and the *International Statistical Classification of Diseases and Health Related Problems,* 10th Revision, 2nd Edition (ICD-10 World Health Organization (WHO), 2004). DCD, which is defined as motor coordination significantly lower than expected for the child's age and intellect, that interferes significantly with activities of daily living, affects approximately 6% of children aged five to 11 years (Maeland, 1992). Both DSM-IV-TR and ICD-10 state that the movement disorder must not be due to a medical (e.g., neurological) condition such as cerebral palsy (CP). If the movement disorder has a neurological component, it is coded on Axis III as a General Medical Condition, rather than on Axis I as a Clinical Disorder. We previously found similar numbers of females and males with DCD (Pearsall-Jones et al., 2008; Skinner & Piek, 2001), as did Foulder-Hughes and Cooke (2003), although other earlier studies have reported a higher incidence of DCD in males (Kadesjö & Gillberg, 1999; Maeland, 1992).

Some 'clumsy' children — especially those with fewer deficits — appear to 'grow out of it' (Cantell et al., 2003); however, others continue to experience difficulties into adulthood (Missiuna et al., 2008). Children with DCD also have been shown to experience psychosocial and academic difficulties (Skinner & Piek, 2001).

DCD has been linked to insult to the developing or immature brain and to premature birth. Foulder-Hughes and Cooke (2003) found that 30.7% of children born preterm possibly met criteria for DCD, compared to 6.7% of children born at term. Jongmans et al. (1998) found that premature infants with extensive perceptual–motor difficulties at 6 years of age were more likely than term infants to have shown a brain lesion shortly after birth. They related this to 'flares', echodensities, or cysts, in the periventricular white matter, which are diagnostic hallmarks of periventricular leukomalacia (PVL), and found that the longer the duration of flares, the worse the motor performance (Jongmans et al., 1993). Episodes of pre- and perinatal hypoxia have also been associated with PVL as a major cause of CP (Wang et al., 2008).

The DSM-IV-TR (APA, 2000) and ICD-10 (WHO, 2004) also have similar classification categories for ADHD and Hyperkinetic Disorder respectively. DSM-IV-TR notes that for a diagnosis of ADHD, inattention and/or hyperactivity must be more frequently displayed and be more severe than is typical for the person's developmental stage, and symptoms must be present before 7 years of age; there must be impairment in two or more settings, and clinically significant impairment must be present in at least one of these — academic, occupational or social functioning.

ADHD has both attentional and movement components. DSM-IV-TR (APA, 2000) has separate diagnostic criteria for symptoms of inattention and hyperactivity/impulsivity, with ADHD diagnosable as three subtypes: Inattentive (ADHD I); Hyperactive/Impulsive (ADHD H/I); and Combined (ADHD C). Both ADHD H/I and ADHD I subtypes require that at least 6 of 9 symptoms specific to those domains be present for diagnosis. ADHD C requires a minimum of 6 symptoms of both ADHD H/I and ADHD I for a diagnosis. It is generally thought to affect some 3% to 10% of school-age children (Wender, 2000), although some estimate the prevalence rate as low as 1% (Swanson et al., 1998). It has been widely reported that more males than females are affected, with estimates in clinical samples varying from 2:1 to 9:1 (APA, 2000).

Investigating the long-term prognosis of ADHD, Mannuzza and colleagues (2000) found that approximately two-thirds to three-quarters of their study participants experienced problematic symptoms of ADHD into early and middle adolescence. Behavioral characteristics of ADHD may remain into adulthood, although symptoms of ADHD may be insufficient to meet DSM-IV-TR (APA, 2000) criteria (Faraone et al., 2006).

Developmental ADHD has been estimated as one of the most heritable disorders of childhood, with approximately twice as many MZ as DZ twin pairs concordant for ADHD (Levy et al., 1997). However, environmental factors, such as brain damage caused by intrauterine infection, forceps delivery, hypoxia or anoxia during pregnancy or at birth, often go unrecognized (Henderson-Smart, 1995; Lou, 1994), and have been linked to secondary ADHD. Lehn et al. (2007) studied MZ twins discordant and concordant for ADHD, and observed that despite the high heritability of ADHD, estimated at 60%, this left 40% to environmental factors. They identified delayed motor development, low birthweight and increased time in an incubator as markers for ADHD in infancy.

Attention deficits and movement disorders have been found to co-occur in close to 50% of cases (Barkley, 1990). For example, Deficits in Attention, Motor Control and Perception (DAMP), has been widely described (Gillberg, 2003). Piek and colleagues (1999) reported an association between inattentive symptomatology and motor ability, particularly fine motor coordination.

The DSM-IV-TR (APA, 2000) specified that, in ADHD, symptomatology involving movement was limited to increased motor activity, and noted that children with ADHD may fall or knock things over, but that this related to impulsivity and distractibility rather than to motor impairment. However, Pitcher and colleagues (2003) provided evidence to suggest

that the motor deficits in ADHD were a result of poor motor ability rather than ADHD symptomatology.

The second-born twin has been found to be at higher risk than the first for poor outcome, for instance, requiring resuscitation or intubation, suffering respiratory distress syndrome, and having a lower 5-minute Apgar (Hartley & Hitti, 2005). Adverse effects of pre-eclampsia, which has been found to be two or three times more common in twin than in singleton pregnancies (Sibai et al., 2000), have been associated with the second-born twin. Blickstein, Ben-Hur and Borenstein (1992) examined 25 twin pregnancies in which the mother had mild pre-eclampsia, 19 in which pre-eclampsia was severe, and 44 controls matched for gestational age (GA). They found that babies whose mothers had severe pre-eclampsia had a significantly shorter GA and lower birthweight compared to those with mild pre-eclampsia. There were three deaths, all second-born twins of mothers with severe pre-eclampsia.

In an earlier study (Pearsall-Jones et al., 2008), we examined questionnaire data on 866 sets of MZ twins, consisting of 23 sets discordant for DCD, 23 sets concordant for DCD, 16 sets discordant for ADHD, 22 sets concordant for ADHD, nine sets in which both twins had both DCD and ADHD, and 773 sets in which neither twin met criteria for either disorder. Given the size of this data set, only questionnaire information could be used as individual assessment of 866 sets of twins was not possible. The aim of the current study was to confirm zygosity using DNA, and to further explore the etiology of movement and attention problems in a smaller sample of MZ twins, using individually administered assessments to confirm diagnosis rather than rely on information from parent questionnaires. Based on the previous study, it was hypothesized that different etiological pathways would be identified for DCD and ADHD, with a relationship found between DCD and perinatal oxygen perfusion problems but not between developmental ADHD and oxygen perfusion problems. Furthermore, it was expected that the second-born twin would be at higher risk for morbidity than the first.

Materials and Method

Participants

Participants were recruited from a large cohort of 2075 sets of twins, of which 866 sets were rated by either parent completed questionnaire, or by DNA, as MZ, or identical twins. From this sample, families with twins discordant or concordant for motor problems or attention problems on the Developmental Coordination Disorder Questionnaire (DCD-Q; Wilson et al., 2000) and the Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN; Swanson et al., 2001) questionnaire respectively (Martin et al., 2006; Pearsall-Jones et al., 2008; Piek et al., 2007), who lived within approximately a 3-hour drive of any capital city in Australia, were sent expressions of interest for participation in a

further stage of the study. Those who consented to participate were interviewed by telephone, during which the ADHD component of the Diagnostic Interview Schedule for Children IV — Parent Interview (DISC-IV-P; Shaffer et al., 2000) was administered to the major caregiver to establish the ADHD status of each young person. After screening for ADHD using the DISC-IV-P and for DCD using questionnaire data from the DCD-Q, 16 sets of twins were eligible to participate. That is, they were considered identical and were aged between 6 and 17 years; they were either discordant or concordant for DCD or ADHD on at least one of the measures, and lived within a 3-hour drive of a capital city. To confirm zygosity, buccal cell DNA was collected and amplified using the ABI profiler plus HID kit (9 DNA markers + sex marker, co-amplified) and separated on a capillary electrophoresis platform using the ABI 3100 instrument. Two female sets of the 16 sets were found to be dizygotic, or fraternal twins, leaving 14 eligible sets.

The average GA at birth was 34.64 weeks, (SD = 2.44; range 31–38 weeks). Nine sets were born ≤ 36 weeks GA, and four sets were born ≤ 32 weeks GA. Average age at time of interview was 13.1 years (SD = 3.65; range 8.17–17.85). Four of the 14 sets were female and 10 sets male. In our study, both twins in a set were delivered either vaginally or by cesarean section. Four sets of twins were born by cesarean delivery. Three mothers reported pre-eclampsia, two of whom had both their twins delivered by cesarean section. Two mothers, including one with severe pre-eclampsia, reported TTTS.

It was decided that regardless of each twin's status on the DCD and ADHD screening instruments, for this study status for disorder would depend on fixed scores as set out in the McCarron Assessment of Neuromuscular Development (MAND; McCarron, 1997) and DISC-IV (Shaffer et al., 2000) manuals. We did this for two reasons. First, on the initial study, rather than use fixed scores on the DCD-Q and SWAN to calculate status as affected or unaffected, individual scores relative to the entire sample of twins determined status (Martin et al., 2006; Pearsall-Jones et al., 2008; Piek et al., 2007). This was not an appropriate method for this small sample. Second, because there was a considerable time lapse between assessments on the two sets of measures, participants who met criteria initially might not at the later date, so discrepancies for status may have reflected actual differences in number of symptoms rather than the validity of the measures.

On the *Wechsler Intelligence Scale for Children — 4th Edition* (WISC-IV — Weschler, 2003), the scores of all twins fell within the *Low Average* (n = 3), *Average* (n = 18), *High Average* (n = 3), *Superior* (n = 3) or *Very Superior* (n = 1) range of intellectual functioning.

On face-to-face assessment for DCD using the MAND, five sets of twins, three male, two female, were discordant for DCD, with 6 or more points dif-

ference (mean = 9.8; *SD* = 3.27; range 6–15) between co-twin scores. In two other female sets, the first-born twin did not meet criteria for DCD, and the second-born had a score of 86, 1 point above the MAND cut-off. Two sets, both male, were concordant for DCD. The concordant twins had the lowest scores on the MAND (mean = 63.5; *SD* = 13.53; range 48–78).

On a parental telephone interview for ADHD using the DISC-IV-P (Shaffer et al., 2000), two male sets of twins were discordant for ADHD, in that one met criteria for a DISC-IV-P diagnosis and the other had neither a *Positive* nor an *Intermediate* diagnosis. Three sets, all male, were neither concordant nor discordant on the DISC-IV-P as either one met criteria for a *Positive* diagnosis and the co-twin met *Intermediate* criteria, or one twin met *Intermediate* criteria and the other was unaffected.

Measures

Developmental Coordination Disorder Questionnaire (DCD-Q)

The DCD-Q (Wilson et al., 2000), a parental report of their child's movement abilities, was included in the Twin and Sibling Questionnaire, the measure initially mailed to families. It includes four subtypes: general coordination; control during movement; gross motor/planning; and fine motor/handwriting. Parents were asked to complete the questionnaire by comparing their child to children of the same age. The total score is 85. Because the Twin and Sibling Questionnaire has a four point scale, to make it easier for parents completing the questionnaire that included the DCD-Q, the 3 was omitted to make a 4-point scale of 1, 2, 4, 5. For inter-item reliability Cronbach's alpha was .88 for the full scale and from .86–.88 for each item if deleted (Martin et al., 2006). Rather than use a fixed score to assign individuals as affected or unaffected, for this measure the cut-off score was calculated using the formula:

$$\text{Cut-off score} = \text{Mean} - (1.65 \times SD).$$

On this scale a low score assigns the participant to the 'affected' group, a high score to the 'unaffected' co-twin control group (Martin et al., 2006; Pearsall-Jones et al., 2008; Piek et al., 2007).

McCarron Assessment of Neuromuscular Development (MAND)

To further explore movement ability, the MAND (McCarron, 1997) was administered during face-to-face assessments. The MAND is a standardized measure developed to assess fine and gross motor development in children aged 3.5 years to young adulthood and above. The measure incorporates five measures of fine motor coordination (e.g., Beads in a Box; Nut and Bolt; Finger Tapping) and five measures of gross motor coordination (e.g., Heel to Toe Walk; Stand on One Foot; Jumping). The scaled scores on each of these are added and the age norms, provided for children aged 3.5 years to young adulthood and above, are used to determine a Neuromuscular Development Index (NDI) with a mean of 100 and standard deviation of 15. A score below 55

is classified as a *severe disability*, 55 to 70 a *moderate disability* and 71 to 85 a *mild disability*. Scores are categorized into four factors: Persistent Control (PC), Muscle Power (MP), Kinesthetic Integration (KI) and Bimanual Dexterity (BD). Test–retest reliabilities after a month interval over the 10 tasks ranged from .67 to .98 (McCarron). Tan et al. (2001), using an Australian sample, found the MAND to have good specificity, good sensitivity and to be a valid measure for the identification of motor impairment.

Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN)

The SWAN (Swanson et al., 2001), is a parental report of their child's attention, impulse control and activity. This instrument is based on the 18 ADHD symptoms listed in the DSM-IV (1994) and involves observations based on the last month in comparison with other children of the same age. Scores for each item range from *Far below average* (scored as +3) to *Far above average* (scored as –3) in order to reflect both strengths and weaknesses. The scores are summed and then divided by nine for the Inattention and Hyperactivity/Impulsivity scale, and by 18 for the Combined subscale, resulting in an average score for each subtype. The cut-offs between individuals affected and unaffected for inattention and hyperactivity/impulsivity are calculated from the distribution of scores using the formula:

$$\text{Cut-off score} = \text{Mean} + (1.65 \times SD).$$

A high score indicates status as 'affected', a low score indicates 'unaffected' (Hay et al., 2007; Martin et al., 2006; Pearsall-Jones et al., 2008; Piek et al., 2007).

The Diagnostic Interview Schedule for Children IV — Parent Interview (DISC-IV-P)

The DISC-IV-P (Schaffer et al., 2000), is a standardized measure designed by the National Institute of Mental Health to assess child and adolescent psychiatric diagnoses by ascertaining presence or absence of symptoms in children and young people aged six to 17 years. The computerized version we used was administered telephonically to the major caregiver, asking questions about the young person. It incorporated a number of impairment questions, to measure the degree to which symptoms significantly impaired or distressed the individual, a criterion required for diagnosis. The DISC-IV-P has eight modules. Only the E (Disruptive Behavior Disorders) ADHD module was administered for purposes of this study. If there were sufficient symptoms causing significant severity/impairment, a DSM-IV (1994) *Positive Diagnosis* was generated. If symptoms were present, but were insufficient or not sufficiently severe to meet DSM-IV diagnosis, an *Intermediate Diagnosis* was made. It has good reliability and validity (Hersen, 2004).

Wechsler Intelligence Scale for Children-IV (WISC-IV) — Australian

The WISC-IV (Weschler, 2003) measures cognitive ability in children aged 6 to 16 years 11 months. This

Table 1

Mean GA, Status on the DISC-IV-P and MAND, and Birth Complications

	Twin 1			Twin 2		
M GA *SD* range	DISC-IV-P	MAND (NDI)	Birth history	DISC-IV-P	MAND (NDI)	Birth history
DCD discordant						
33.4 (2.51) 31–37	N	N (93)	Mother pre-eclampsia	N	Y (78)	Mother pre-eclampsia
	N	N (89)		N	Y (80)	Oxygen perfusion problems
	N	Y (84)	Oxygen perfusion problems	I	N (93)	
	I	N (93)		N	Y (83)	
	N	N (88)	Oxygen perfusion problems	I	Y (82)	Oxygen perfusion problems
DCD concordant						
33.5 (3.54) 31–36	I	Y (78)	Oxygen perfusion problems; TTTS	Y (CT)	Y (71)	Oxygen perfusion problems; TTTS
	I	Y (57)	Oxygen perfusion problems	Y (IT)	Y (48)	Oxygen perfusion problems
MAND second twin 86						
35.5 (2.12) 34–37	N	N (104)		I	N (86)	Oxygen perfusion problems
	I	N (94)	Mother pre-eclampsia	I	N (86)	Mother pre-eclampsia
ADHD Discordant						
36 (2.83) 34–38	N	N (101)		Y (IT)	N (87)	
	N	N (111)		Y (CT)	N (94)	
ADHD Intermediate and/or Positive diagnoses						
36 (1.73) 34–37	I	N (95)	Oxygen perfusion problems; TTTS; mother severe pre-eclampsia	Y (CT)	N (90)	Oxygen perfusion problems; TTTS; mother severe pre-eclampsia
	Y (IT)	N (99)		I	N (95)	
	I	N (111)		N	N (111)	

Note: Y = diagnosis present; N = diagnosis absent; I = intermediate diagnosis; CT = combined type; IT = inattentive type

was administered to ensure that participants met DSM-IV-TR (2000) criteria for DCD, which requires motor coordination to be significantly lower than expected for the child's intellect, and to ascertain whether there were significant differences in intellectual ability between first- and second-born twins. The 10 core subtests yield four subtest indices: Verbal Comprehension (VCI), Perceptual Reasoning (PRI), Working Memory (WMI), and Processing Speed (PSI). These subtests were administered for the purposes of this study.

The WISC-IV has excellent internal consistency, test-retest reliability, and criterion and construct validity. Reliability coefficients for the WISC-IV Australian subtests averaged from .75 to .89.

Behavioral Assessment System for Children Structured Developmental History (BASC-SDH)

Mothers were asked to complete the BASC SDH (Reynolds & Kamphaus, 2004). This was to gather more extensive information on birth complications and developmental history. This survey provides a detailed birth, medical and developmental history, contextualising the young person's behavior.

Procedure

The project was approved by the Curtin University of Technology Human Research Ethics Committee and by the Australian Twin Registry (ATR). Following written consent by parents and assent by young people the parents were contacted and the DISC-IV-P (Schaffer et al., 2000) was administered telephonically. Appointments were made to visit the homes of 15 sets of the 16 sets identified prior to DNA confirmation of zygosity. One set chose to be interviewed at Curtin University of Technology.

Twins in a set were interviewed by different researchers — one assessing one twin whilst the other assessed the other. Assessors were blind to the participant's DCD and ADHD status. Administration time varied between five and seven hours, with several breaks in between. Three sets of twins had their status as monozygotic confirmed by DNA analysis prior to our study. The remaining 13 sets were mailed kits to collect buccal cells for DNA analysis. The DNA of two sets of female twins indicated that they were dizygotic or fraternal twins. Data on these twins were excluded from data analysis.

Results

DCD and ADHD

Table 1 shows case by case twin status for DCD and ADHD on the DISC-IV-P and MAND, and provides the relevant birth history. It is broken down into

Table 2

Comparisons Between First- and Second-Born Twins for Birthweight and 1- and 5-Minute Apgar Dcores Using 1-Tailed Paired *t* Tests; and on the MAND, C-DISC IV, and WISC-IV Using 2-Tailed Paired *t* Tests

		First-born	Second-born	Both twins		
Measure	Variable	M (SD)	M (SD)	Range	*t*	*p*
Birth demographics	Weight (gms)	2208 (475)	2228 (401)	1448–3005	−.26	.4
	1 min Apgar	8.22 (.97)	7.11 (1.27))	6–9	1.89	.048*
	5 min Apgar	8.8 (.79)	8.6 (.52)	7–10	1	.17
MAND	Fine motor	41.64 (13.19)	36.93 (12.31)	5–65	1.77	.1
	Gross motor	44.08 (8.6)	39.62 (11.51)	9–68	2.9	.012*
	NDI	92.64 (13.91)	84.57 (14.15)	48–111	4.26	.001*
	PC	18.43 (5.16)	17.21 (6.96)	0–27	.69	.5
	MP	17.29 (6.56)	15.5 (8.22)	2–35	1.23	.24
	KI	19 (5.81)	16.86 (7.15)	0–26	2.15	.05
	BD	17.21 (6.24)	14.36 (5.75)	0–25	2.4	.032*
DISC-IV-P	Number ADHD symptoms	4 (3.64)	6.29 (5.98)	0–18	1.35	.2
WISC-IV	VCI	110.21 (12.81)	108.14 (15.84)	81–138	.77	.45
	PRI	104.29 (11.73)	102.36 (14.93)	67–133	.51	.62
	WMI	104.36 (19.94)	104.14 (11.26)	86–146	.05	.96
	PSI	95.07 (10.37)	91.93 (9.79)	75–112	.88	.39
	FSIQ	105.43 (12.17)	102.86 (12.74)	84–138	.93	.37

groups with age means: DCD Discordant (13.3 years; *SD* = 2.93; range 8.42–15.58); DCD Concordant (12.8 years; *SD* = 5.54; range 8.33–16.67); MAND second twin 86 (9.13 years; *SD* = .64; range 8.67–9.58); ADHD discordant (13.63 years; *SD* = 1.29; range 13.17–14.09); and ADHD sets with *Positive* and *Intermediate* diagnoses (13.95 years; *SD* = 5.11; range 8.17–17.85). Because of the small numbers in the groups, mean age comparisons were not made.

Of the four sets of twins born ≤ 32 weeks GA, two first-born twins (one of whom was born with a cord around the neck), and three second-born twins, had MAND scores < 85. At birth, three first-born twins and five second-born twins required oxygen supplements for a period longer than 2 hours to 11 weeks (some twins required oxygen for a 'few minutes' to 1 or 2 hours — this was not regarded as indicating oxygen perfusion problems).

All three first-born twins with DCD on the MAND experienced perinatal oxygen perfusion problems (two required oxygen at birth, one for 11 weeks; the mother of one reported pre-eclampsia; a third was born with a cord around the neck). Four of the six second-born twins with DCD on the MAND experienced perinatal oxygen perfusion problems (three required oxygen at birth, one for 8 weeks; the fourth had breathing difficulties); one mother reported pre-eclampsia. Two second-born twins had scores of 86 on the MAND — the mother of one reported pre-eclampsia; the other twin was reported as having severe breathing difficulties and required supplementary oxygen. Both twins in both sets concordant for DCD experienced perinatal oxygen perfusion problems, and one set experienced TTTS. Both second-born twins

in these sets also met criteria for a *Positive* diagnosis of ADHD (one Combined, one Inattentive), and both first-born twins' scores placed them in the *Intermediate* range for ADHD.

A total of six twins were diagnosed with ADHD based on the DISC-IV-P, one first-born (Combined) and five second-born twins (two Inattentive, three Combined). Three of these (all second-born twins) experienced oxygen perfusion problems. An additional 11 twins — the co-twins of four of whom were *Positive* for ADHD — had DISC-IV-P scores placing them in the *Intermediate* range for ADHD, indicating that they had attention problems which were insufficient to warrant a *Positive* diagnosis. Six were first-born and five second-born twins, and only two of these, both second-born, experienced perinatal oxygen perfusion problems. The only twins who met criteria for both DCD and ADHD were the two second-born twins in the DCD concordant group.

First vs. Second Twin

Table 2 shows first and second-born twin average birthweights and scores on Apgar (one-tailed paired *t* tests) and scores on the MAND, DISC-IV-P, and WISC-IV (two-tailed paired *t* tests). There were statistically significant differences between first- and second-born twins on 1-minute Apgar, and on the MAND Gross Motor, Bimanual Dexterity and Neuromuscular Developmental Index, in favor of first-born twins.

Discussion

This study was designed primarily to further examine the etiology of DCD and ADHD, and to explore

whether the second-born twin was at higher risk than the first-born for adverse events pre- and perinatally.

There were similar numbers of males and females in the DCD discordant group. We previously found similar numbers of males and females with DCD (Pearsall-Jones et al., 2008; Skinner & Piek, 2001), as did Foulder-Hughes and Cooke (2003), although other studies have found more males than females (Kadesjö & Gillberg, 1999; Maeland, 1992). There were only two sets of twins, both male, in the DCD concordant group.

All six twins who met criteria for a *Positive* diagnosis of ADHD were male. We previously found more males than females with ADHD (Pearsall-Jones et al., 2008), as has been reported elsewhere (Rhee et al., 2001). Rhee and colleagues concluded that males were more likely than females to be affected by ADHD as, genetically, males have a lower threshold for the required liability to express ADHD.

All three first-born twins and four of the six second-born twins with DCD on the MAND experienced birth complications including oxygen perfusion problems perinatally, in another the mother reported pre-eclampsia. Of the two second-born twins who had scores one point above the DCD cut-off on the MAND, one mother reported pre-eclampsia; the other affected twin had severe perinatal breathing difficulties and required supplementary oxygen. The current study thus found an association between perinatal oxygen perfusion problems and DCD, as we found previously on a larger study using questionnaire data only (Pearsall-Jones et al., 2008). In our studies it was not clear whether movement difficulties in these twins resulted from perinatal oxygen perfusion problems, or whether, as proposed by Gunn and Bennet (2008), exposure to infections in utero cumulatively sensitized them to hypoxia at birth, or because of prenatal cardiac or lung problems leading to perinatal oxygen perfusion problems (Morley, 2005). In neonatal hypoxic-ischemic encephalopathy, 20–30% of survivors were estimated to have long term neurodevelopmental sequelae, including CP (Vannucci & Perlman, 1997).

Although there is little literature on the etiology of DCD, most of what is available suggests that environmental factors, for instance brain lesions (Jongmans et al., 1998) and flares (Jongmans, 1993), are likely to be the major cause of damage to the developing brain. There were no reports from parents participating in our study of brain scans on their twins shortly after birth, so the possibility of brain lesions and 'flares' could not be explored. In our study, of the three mothers who reported pre-eclampsia, two delivered at 34 weeks, the other at 35 weeks. Previous research has shown that mothers with twin pregnancies with gestational hypertension (hypertension without proteinuria) had more twins delivered < 37 weeks and < 35 weeks, and more babies who were small for GA. Bdolah and colleagues (2008) found that the larger placenta of a twin compared to a singleton pregnancy resulted in higher rates of angiogenic proteins, and that this contributed to the risk for pre-eclampsia. One of the two sets of DCD concordant twins experienced TTTS in utero, which can cause ischemic damage at various stages of pregnancy (Pharoah, 2006).

If neurological conditions are a primary etiology of DCD, then DCD and CP may fall on a continuum of movement disorder. This is important, as DSM-IV-TR (APA, 2000) and ICD-10 (WHO, 2004) diagnostic criteria specify that if a general medical (e.g. neurological) condition is present, the movement disorder is coded on Axis III as a General Medical Condition, rather than on Axis I as a Clinical Disorder. With advances in neuroimaging and other scientific developments, the etiology of wellness and illness is less mysterious than was the case even relatively recently. If DCD is a result of a medical condition, DSM-IV-TR and ICD-10 diagnostic criteria might need to be revised. Second, and consequent to this, in some instances a diagnosis of mild CP, rather than DCD, may make young people with DCD eligible for services currently reserved for young people with CP and their families. This could facilitate early treatment, as recommended in Piek (2006).

None of the five sets of twins discordant for DCD also met criteria for a *Positive* diagnosis of ADHD, although three twins met criteria for an *Intermediate* diagnosis. Of the two sets of twins who were concordant for DCD, both second-born twins also met criteria for a *Positive* diagnosis for ADHD (one Combined, one Inattentive), and both first-born twins' scores placed them in the *Intermediate* range for ADHD. By contrast, previous studies have shown a close association between movement disorders and ADHD (Gillberg, 2003; Martin et al., 2006; Piek et al., 1999).

One first and five second-born twins met the DISC-IV-P (Shaffer et al., 2000) criteria for ADHD, and four of their co-twins were *Intermediate* for ADHD. None of the twins discordant for ADHD experienced perinatal oxygen perfusion problems. Of the six twins who met criteria for ADHD, only the two second-born DCD concordant sets had co-occurring ADHD, and both experienced perinatal oxygen perfusion problems. This raises the issue of secondary ADHD, with environmental etiology, as opposed to developmental ADHD with a genetic etiology, and whether the etiology of ADHD in the DCD concordant twins is secondary to intrauterine infection and anoxia or hypoxia at birth (Henderson-Smart, 1995; Lou, 1994), as has been previously suggested (Pearsall-Jones et al., 2008). The DCD concordant twins were the most severely affected in terms of their motor deficits, further supporting the view that there was more extensive damage that may also be associated with ADHD. This suggests that it is important to further explore the nature of movement deficits associated with developmental and secondary ADHD, and the nature of

attention deficits associated with DCD. All of the young people in our study with ADHD had an Inattentive component. In cases in which discordance for ADHD cannot be associated with birth complications or other medical factors in affected twins, epigenetic processes affecting only one twin might be a possibility, as found by Bennett and colleagues (2008) in hemophilia A.

On paired t tests, the 1-minute Apgar score of the second-born twin was significantly lower than that of the first-born twin. Lower 5-minute Apgar scores in second- than first-born twins have previously been found (Hartley & Hitti, 2005), with the second-born twin at higher risk for requiring resuscitation or intubation, and for suffering respiratory distress syndrome. Montassir and colleagues (in press) have associated perinatal oxygen perfusion difficulties and low 1-minute Apgar with hypoglycemic brain lesions and CP. Three first- and six second-born twins met MAND criteria for DCD, suggesting that second-born twins were at higher risk for movement disorder than first-born twins. Second-born twins performed at a significantly lower level than first-born twins on MAND Gross Motor, Bimanual Dexterity and the Neuromuscular Developmental Index. Previous studies have concluded that second-born twins were at higher risk for morbidity than first-born twins (Hartley & Hitti, 2005). In our study this could not be linked with type of delivery, as in no case was the first twin delivered vaginally and the second by cesarean delivery.

There were no significant differences between first- and second-born twins on the WISC-IV, so second-born twins were not significantly more intellectually compromised than first-born twins. This is consistent with previous studies (Ramsey et al., 2000; Tinca et al., 2006).

Future Research

Establishing the etiology of DCD and ADHD, and the role of environmental and epigenetic processes in discordant MZ twins, has significant implications for clinical practice and perhaps for prevention. Assessment, using the MAND, of young people with mild CP will help clarify whether the patterns of movement disorder in mild CP and DCD are similar. Current research underway in Australia is investigating the association between movement disorders, specifically CP, genes and susceptibility to infections in utero. If such genes are identified, a project could be undertaken to establish whether children with DCD have similar genetic vulnerabilities, which may be related to oxygen perfusion difficulties at birth. Whether the relationship is causal or by association, for instance reflecting a prenatal insult or aberration involving the lungs or brain which depresses ability to oxygenate at birth, is beyond the scope of this paper.

Some neonates who have experienced perinatal asphyxia have developed movement disorders, including CP (Vannucci & Perlman, 1997; Morley, 2005;

Westin, 2006). Neonatal induced hypothermia might also be further explored, as this has been shown to improve outcome for neonates experiencing perinatal asphyxia (Jacobs et al., 2007; Lin et al., 2006). Permissive hypercapnia has also been found to be of benefit in neonates with respiratory disease and brain injury who experience severe hyper and hypocapnia (Zhou & Liu, 2008).

Creation of, and access to, twin registers and databases, for instance the WA Twin Child Health (WATCH) register, with links to databases such as the Western Australia Maternal and Child Health Database (Croft et al., 2002), would provide a more detailed birth history to supplement caregiver recall.

Conclusions

In the current study we used a co-twin control design to investigate etiological pathways for DCD and ADHD. This was found to be a very effective design as it identified unique environmental factors that could be linked to specific disorders. In particular, DCD was found to be associated with perinatal oxygen perfusion problems that were not present for developmental ADHD. Furthermore, being a second-born twin was also linked with poorer motor outcome but not on average with increased inattention nor hyperactivity/impulsivity. However, given the small number of twins that can be identified using this approach, these findings need to be examined further with studies using both the discordant co-twin control design as well as other suitable approaches.

Acknowledgments

References

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text revision). Washington, DC: Author.

Barkley, R. (1990). *Attention deficit disorder: A handbook for diagnosis and treatment.* New York: Guilford Press.

Bennett, C. M., Boye, E., & Neufeld, E. J. (2008). Female monozygotic twins discordant for hemophilia A due to nonrandom X-chromosome inactivation. American *Journal of Hematology, 83*, 778–780.

Bdolah, Y., Lam, C., Rajakumar, A., Shivalingappa, V., Mutter, W., Sachs, B. P., Lim, K. H., Bdolah-Abram, T., Epstein, F. H., & Karumanchi, S. A. (2008). Twin pregnancy and the risk of preeclampsia: bigger pla-

centa or relative ischemia? *American Journal of Obstetrics & Gynecology, 198,* 428–430.

Bjelic-Radisic, V., Pristauz, G., Haas, J., Giuliani, A., Tamussino, K., Bader, A., Lang, U., & Schlembach, D. (2007). Neonatal outcome of second twins depending on presentation and mode of delivery. *Twin Research and Human Genetics, 10,* 521–527.

Blickstein, I., Ben-Hur, H., & Borenstein, R. (1992). Perinatal outcome of twin pregnancies complicated with preeclampsia. *American Journal of Perinatology, 9,* 258–260.

Brown, C. J., & Robinson, W. P. (2000). The causes and consequences of random and non-random X chromosome inactivation in humans. *Clinical Genetics, 58,* 353–363.

Cantell, M. H., Smyth, M. M., & Ahonen, T. P. (2003). Two distinct pathways for developmental coordination disorder: Persistence and resolution. *Human Movement Science, 22,* 413–431.

Croft, M. L., Read, A. W., de Klerk, N. H., Hansen, J., & Kurinczuk, J. J. (2002). Population based ascertainment of twins and their siblings born in Western Australia 1980 to 1992, through the construction and validation of a maternally linked database of siblings. *Twin Research, 5,* 317–323.

Duliège, A. M., Amos, C. I., Felton, S., Biggar, R. J., & Goedert, J. J. (1995). Birth order, delivery route, and concordance in the transmission of human immunodeficiency virus type 1 from mothers to twins. International Registry of HIV-Exposed Twins. *Pediatrics, 126,* 625–632.

Faraone, S.V., Biederman, J., & Mick, E. (2006). The age-dependent decline of attention deficit hyperactivity disorder: A meta-analysis of follow-up studies, *Psychological Medicine, 36,* 159–165.

Foulder-Hughes, L. A., & Cooke, R. W. (2003). Developmental co-ordination disorder in preterm children born ≤ 32 weeks gestational age. *Dyspraxia Foundation Professional Journal, l,* 3–13.

Forrester, R. M., Lees, V. T., & Watson, G. H. (1966). Rubella syndrome: Escape of a twin. *British Medical Journal, 1,* 1403.

Fraga, M. F., Ballestar, E., Paz, M. F., Ropero, S., Setien, F., Ballestar, M. L., Heine-Suñer, D., Cigudosa, J. C., Urioste, M., Benitez, J., Boix-Chornet, M., Sanchez-Aguilera, A., Ling, C., Carlsson, E., Poulsen, P., Vaag, A., Stephan, Z., Spector, T. D., Wu, Y. Z., Plass, C., & Esteller, M. (2005). Epigenetic differences arise during the lifetime of monozygotic twins. *Proceedings of the National Academy of Sciences USA, 102,* 10604–10609.

Gillberg, C. (2003). Deficits in attention, motor control, and perception: A brief review. *Archives of Disease in Childhood, 88,* 904–910.

Gunn, A. J., & Bennet, L. (2008). Timing of injury in the fetus and neonate. *Current Opinions in Obstetrics and Gynecology, 20,* 175–181.

Hartley, R. S., & Hitti, J. (2005). Birth order and delivery interval: Analysis of twin pair perinatal outcomes. *Journal of Maternal-Fetal and Neonatal Medicine, 1,* 375–380.

Hay, D. A., Bennett, K. S., Levy, F., Sergeant, J., & Swanson, J. (2007). A twin study of attention-deficit/hyperactivity disorder dimensions rated by the strengths and weaknesses of ADHD-symptoms and normal-behavior (SWAN) scale. *Biological Psychiatry, 61,* 700–705.

Henderson-Smart, D. J. (1995). Postnatal consequences of chronic intrauterine compromise. *Reproduction, Fertility and Development, 7,* 559–565.

Hersen, M. (Editor-in-Chief) (2004). *Comprehensive handbook of psychological assessment.* Hoboken, NJ: Wiley & Sons.

Iwayama, H., Hosono, H., Yamamoto, H., Oshiro, M., & Ueda, N. (2007). Aplasia cutis congenital with skull defect in a monozygotic twin after exposure to methimazole in utero. *Birth Defects Research (Part A): Clinical and Molecular Teratology, 79,* 680–684.

Jacobs, S., Hunt, R., Tarnow-Mordi, W., Inder, T., & Davis, P. (2007). Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Systematic Review, 17,* CD003311.

Jongmans, M., Henderson, S., de Vries, L., & Dubowitz L. (1993). Duration of periventricular densities in preterm infants and neurological outcome at 6 years of age. *Archives of Disease in Childhood, 69,* 9–13.

Jongmans, M. J., Mercuri, E., Dubowitz, L. M. S., & Henderson, S. E. (1998). Perceptual-motor difficulties and their concomitants in six-year-old children born prematurely. *Human Movement Science, 17,* 629–653.

Kadesjö, B., & Gillberg, C. (1999). Developmental coordination disorder in Swedish 7-year-old children. *Journal of the American Academy of Child and Adolescent Psychiatry, 38,* 820–828.

Lehn, H., Derks, E. M., Hudziak, J. J., Heutink, P., van Beijsterveldt, T. C., & Boomsma, D. I. (2007). Attention problems and attention-deficit/hyperactivity disorder in discordant and concordant monozygotic twins: Evidence of environmental mediators. *Journal of the American Academy of Child and Adolescent Psychiatry, 46,* 83–91.

Levy, F., Hay, D. A., McStephen, M., Wood, C., & Waldman, I. (1997). Attention-deficit hyperactivity disorder: A category or a continuum? Genetic analysis of a large-scale twin study. *Journal of the American Academy of Child and Adolescent Psychiatry, 36,* 737–744.

Lin, Z. L., Yu, H. M., Lin, J., Chen, S. Q., Liang, Z. Q., & Zhang, Z. Y. (2006). Mild hypothermia via selective head cooling as neuroprotective therapy in term neonates with perinatal asphyxia: An experience from a single neonatal care unit. *Journal of Perinatology, 26,* 180–184.

Lou, H. C. (1994). Hypoxic-hemodynamic pathogenesis of brain lesions in the newborn. *Brain and Development, 16,* 423–431.

Machin, G., Still, K., & Lalani, T. (1996). Correlations of placental vascular anatomy and clinical outcomes in 69 monochorionic twin pregnancies. *American Journal of Medical Genetics Part A*, 61, 229–236.

Maeland, A. F. (1992). Identification of children with motor coordination problems. *Adapted Physical Activity Quarterly, 9,* 330–342.

Mannuzza, S., & Klein, R. G. (2000). Long-term prognosis in attention-deficit/hyperactivity disorder. *Child and Adolescent Psychiatric Clinics of North America, 9,* 711–726.

Martin, N., Boomsma, D., & Machin, G. A. (1997). A twin-pronged attack on complex traits. *Nature Genetics, 17,* 387–392.

Martin, N. C., Piek, J. P., & Hay, D. A. (2006). DCD and ADHD: A genetic study of their shared etiology. *Human Movement Science, 25*, 110–124.

McCarron, L. T. (1997). *McCarron assessment of neuromuscular development: fine and gross motor abilities — Revised.* Dallas: McCarron-Dial Systems, Inc.

Missiuna, C., Moll, S., King, G., Stewart, D., & Macdonald, K., (2008). Life experiences of young adults who have coordination difficulties. *Canadian Journal of Occupational Therapy, 75*, 157–166.

Montassir, H., Maegaki, Y., Ogura, K., Kurozawa, Y., Nagata, I., Kanzaki, S., & Ohno, K. (in press). Associated factors in neonatal hypoglycemic brain injury. *Brain and Development.*

Morley, G. M. (2005). Birth brain injury: Etiology and prevention Part I: Hypoxic-ischemic encephalopathy and cerebral palsy. *Medical Veritus, 2,* 500–506.

Pearsall-Jones, J. G., Piek, J. P., Martin, N. C., Rigoli, D., Levy, F., & Hay, D. A. (2008). A monozygotic twin design to investigate etiological factors for DCD and ADHD. *Journal of Pediatric Neurology, 6,* 209–219.

Pharoah, P. O. (2006). Twins and locomotor disorder in children. *Journal of Bone and Joint Surgery — British Volume, 88,* 295–297.

Piek J. P. (2006). *Infant motor development.* Champaigne, IL: Human Kinetics.

Piek, J. P., Pitcher, T. M., & Hay, D. A. (1999). Motor coordination and kinaesthesis in boys with attention deficit-hyperactivity disorder. *Developmental Medicine and Child Neurology, 41,* 159–165.

Piek, J. P., Rigoli, D., Pearsall-Jones, J. G., Martin, N. C., Hay, D. A., Bennett, K. S., & Levy, F. (2007). Depressive symptomatology in child and adolescent twins with attention-deficit hyperactivity disorder and/or developmental coordination disorder. *Twin Research and Human Genetics, 10,* 587–596.

Pitcher, T. M., Piek, J. P., & Hay, D. A. (2003). Fine and gross motor ability in males with ADHD. *Developmental Medicine and Child Neurology, 45,* 525–535.

Race, J. P., Townsend, G. C., & Hughes, T. E. (2006). Chorion type, birthweight discordance and tooth-size variability in Australian monozygotic twins. *Twin Research and Human Genetics, 9,* 285–291.

Ramsey, P. S., Hou, J., Cliver, S. P., Nelson, K. G., Ramey, S. L., & Goldenberg, R. L. (2000). Five-year comparative anthropometric and neurologic outcomes of first vs. second-born twins. *American Journal of Obstetrics & Gynecology, 182,* S148.

Reynolds, C. R., & Kamphaus, R. W. (2004). *Behavioral Assessment System for Children. Structured Developmental History.* Circle Pines, MN: AGS Publishing.

Rhee, S. H., Waldman, I. D., Hay, D. A., & Levy, F. (2001). Etiology of the sex differences in the prevalence of DSM-III-R ADHD: A comparison of two models. In F. Levy & D. A. Hay (Eds), *Attention, genes and ADHD* (pp. 139–156). Hove: Brunner-Routledge.

Shaffer, D., Fisher, P., Lucas, C. P., Dulcan, M. K., & Schwab-Stone, M. E. (2000). NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): Description, differences from previous versions, and reliability of some common diagnoses. *Journal of the American Academy of Child and Adolescent Psychiatry, 39*, 28–38.

Sibai, B. M., Hauth, J., Caritis, S., Lindheimer, M. D., MacPherson, C., Klebanoff, M., VanDorsten, J. P., Landon, M., Miodovnik, M., Paul, R., Meis, P., Thurnau, G., Dombrowski, M., Roberts, J., & McNellis, D. (2000). Hypertensive disorders in twin versus singleton gestations. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *American Journal of Obstetrics & Gynecology, 182*, 938–942.

Skinner, R. A., & Piek, J. P. (2001). Psychosocial implications of poor motor coordination in children and adolescents. *Human Movement Science, 20*, 73–94.

Smith, G. C., Fleming, K. M., & White, I. R. (2007). Birth order of twins and risk of perinatal death related to delivery in England, Northern Ireland, and Wales, 1994–2003: Retrospective cohort study. *British Medical Journal*, 334, 576.

Sperber, G. H., Machin, G. A. & Bamforth, F. J. (1994). Mirror-image dental fusion and discordance in monozygotic twins. *American Journal of Medical Genetics, 51,* 41–45.

Swanson, J., Castellanos, F. X., Murias, M., LaHoste, G., & Kennedy, J. (1998). Cognitive neuroscience of attention deficit hyperactivity disorder and hyperkinetic disorder. *Current Opinions in Neurology, 8,* 263–271.

Swanson, J., Schuck, S., Mann, M., Carlson, C., Hartman, K., & Sergeant, J. (2001). *The SWAN rating scale.* Available at http://www.adhd.net

Tan, S. K., Parker, H. E., & Larkin, D. (2001). Concurrent validity of motor tests used to identify children with motor impairment. *Adapted Physical Activity Quarterly, 18*, 168–182.

Tinca, J. C. P., Polderman, T. J. C., Gosso, M. F., Posthuma, D., Van Beijsterveldt, T. C. E. M., Heutink, P., Verhulst, F. C., & Boomsma, D. I. (2006). A longitudinal twin study on IQ, executive functioning, and attention problems during childhood and early adolescence. *Acta Neurologica Belgica, 106,* 191–207.

Vannucci, R. C., & Perlman, J. M. (1997). Interventions for perinatal hypoxic-ischemic encephalopathy. *Pediatrics, 100,* 1004–1014.

Wang, T., Zhang, L., Jiang, L., & He, N. (2008). Neurotoxicological effects of 3-nitropropionic acid on the neonatal rat. *Neurotoxicology, 29,* 1023–1029.

Wechsler, D. (2003). *Wechsler Intelligence Scale for Children — 4th ed.* San Antonio, TX: The Psychological Corporation.

Wender, P. H. (2000). *Attention deficit hyperactivity disorder in children and adults.* New York: Oxford University Press.

Westin, B. (2006). Hypothermia in the resuscitation of the neonate: A glance in my rear-view mirror. *Acta Paediatrica, 95,* 1172–1174.

Wilson, A. G. (2008). Epigenetic regulation of gene expression in the inflammatory response and relevance to common diseases. *Journal of Periodontology, 79,* 1514–1519.

Wilson, B. N., Kaplan, B. J., Crawford, S. G., Campbell, A., & Dewey, D. (2000). Reliability and validity of a parent questionnaire on childhood motor skills. *American Journal of Occupational Therapy, 54,* 484–493.

World Health Organization. (2004). *International statistical classification of diseases and health related problems, 10th revision* (2nd ed.). Geneva: Author.

Zhou, W., & Liu, W. (2008). Hypercapnia and hypocapnia in neonates. *World Journal of Pediatrics, 4,* 192–196.