Aus der Klinik für Neonatologie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Handedness of former preterm infants < 1000 grams birth weight, association with neonatal complications and cognition at 5 years of age

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List of abbreviations

BPD	= Bronchopulmonary Dysplasia
BH	= Both Hands / Ambidextrous
ELBW	= Extremely Low Birth Weight (Birth Weight < 1000 g)
GA	= Gestational Age
H-D-T	= Handedness Dominance Test
HAPT4-6	= Hand Preference Test for 4- to 6-year-olds
IVH	= Intraventricular Hemorrhage
K-ABC	= Kaufmann Assessment Battery for Children
NEC	= Necrotizing Enterocolitis
NRH	= Non-right-handed
P - Value	= Significance
PTK-LDT	= Puncture Test and Performance Dominance Test
PVL	= Periventricular Leukomalacia
RH	= Right-handed
VLBW	= Very Low Birth Weight (Birth Weight < 1500 g)
WOP	= Weeks of Pregnancy

Abstract

Facts: A Lancet article by O'Callaghan et al. from 1987 initiated the discussion about an increased rate of non-right-handedness in "extremely low birth weight" (ELBW, < 1000 g) children by showing a rate of left-handedness as high as 54% in these early born babies. Further studies from the nineties widely supported such an increase in left-handedness in former ELBW infants and found a correlation between the handedness of these preterm children and the occurrence of neonatal morbidities, in particular severe cerebral abnormalities. Moreover, contradictory results concerning a relation between handedness and cognition in ELBW infants have been published. As a result of the major improvements in perinatal medicine during the past two decades, the mortality of ELBW children has decreased substantially, with significantly more children surviving and thus altering the composition of the ELBW cohort.

Purpose: The aim of this retrospective study was to re-examine the hypothesis of an increased prevalence of non-right-handedness in extremely preterm children by investigating handedness in a contemporary, local ELBW population. The study also addressed the suspected association between handedness and neonatal complications and examined the controversial relation between handedness and cognitive deficits.

Methods: Data of an ELBW cohort was obtained from the medical records of 229 surviving ELBW infants born between 2004 and 2007 at the Charité University Medical Center, Campus Virchow Klinikum. Information about handedness, neonatal morbidities and cognitive abilities (using the results of the Kaufmann Assessment Battery for Children) was gathered by reviewing such files. Infants with grade 4 intraventricular hemorrhage were excluded and the study cohort was divided into 3 subgroups for further investigations. For comparison, reference group data was provided by the Berlin Senate Department of Health and Social Services. All data was statistically analyzed using SPSS.

Results: The ELBW cohort of this study showed an increased prevalence of non-right-handedness, which was confirmed in the comparison group. The increase was significantly lower compared to the rate described by O'Callaghan et al. in 1987. Male ELBW children were significantly more likely to be left-handed than female ones. There was no statistically significant association between cognition and handedness or between neonatal morbidities and handedness.

Conclusion: The hypothesis of an increased rate of non-right-handedness in ELBW infants can be confirmed by this study. There was no link between handedness and cognitive scores.

Zusammenfassung

Hintergrund: Ein Lancetartikel von O‘Callaghan et al. aus dem Jahre 1987, welcher eine Prävalenz der Linkshändigkeit von 54% bei „extremely low birth weight“ (ELBW, < 1000 g) Frühgeborenen aufzeigte, löste Diskussionen über ein vermehrtes Auftreten von Nichtrechtshändigkeit bei ELBW-Frühgeborenen aus. Weitere Studien aus den neunziger Jahren stützten diese These und konnten zudem einen Zusammenhang zwischen der Händigkeit von ELBW-Frühgeborenen und dem Auftreten von neonatalen Erkrankungen aufzeigen. Bezüglich eines Zusammenhangs zwischen Händigkeit und Kognition hingegen liegen widersprüchliche Daten vor. Aufgrund zahlreicher Fortschritte in der perinatalen Medizin in den letzten zwanzig Jahren konnte die Frühgeborenensterblichkeit spürbar gesenkt werden, so dass heute deutlich mehr Kinder überleben, was sich auf die Charakteristika der ELBW-Kohorte auswirkt.

Studienziel: Das Ziel dieser Studie war die Überprüfung der These, der zufolge ELBW-Frühgeborene eine vermehrte Nichtrechtshändigkeit aufweisen, innerhalb einer aktuellen ELBW-Kohorte. Zusätzlich sollte der Zusammenhang zwischen Händigkeit und neonatalen Erkrankungen sowie zwischen Händigkeit und kognitiven Defiziten überprüft werden.

Methodik: Die Daten der Studienkohorte wurden durch eine Sichtung und Auswertung der Krankenakten von 229 ELBW-Frühgeborenen, welche in den Jahren 2004 bis 2007 in der Neonatologie der Charité am Standort Campus Virchow Klinikum geboren wurden, erhoben. Es wurden Informationen über die Händigkeit, neonatale Erkrankungen und die IQ-Ergebnisse des Kaufmann Assessment Battery for Children (K-ABC) - Intelligenztests der Kinder erfasst. Kinder mit intraventrikulärer Hämorrhagie Grad IV wurden ausgeschlossen und die Kohorte wurde für weitere Untersuchungen in 3 Subgruppen unterteilt. Zum Vergleich wurden von der Senatsverwaltung für Gesundheit und Soziales Berlin Daten für eine Referenzgruppe bereitgestellt. Sämtliche Daten wurden mit SPSS statistisch ausgewertet.

Ergebnisse: Auch die ELBW-Frühgeborenen der hiesigen Studienkohorte und die Vergleichsgruppe zeigten eine erhöhte Prävalenz der Linkshändigkeit, welche allerdings signifikant geringer war als die von O‘Callaghan et al. nachgewiesene Auftretenswahrscheinlichkeit im Jahre 1987. Männliche ELBW-Frühgeborene zeigten zudem signifikant häufiger Nichtrechtshändigkeit als Mädchen. Es wurde kein Zusammenhang zwischen Händigkeit, Kognition und neonatalen Erkrankungen gefunden.

Schlussfolgerung: Die These einer erhöhten Prävalenz von Linkshändigkeit in ELBW Frühgeborenen bestätigte sich, ohne dass sich eine Assoziation mit neonatalen Erkrankungen oder den späteren kognitiven Fähigkeiten zeigte.

1 Introduction

1.1 Handedness – current state of research

1.1.1 Asymmetries of the brain: Cerebral lateralization and handedness

As described by Porac and Coren, all paired sense organs and limbs are morphologically similar, except for slight structural asymmetries, as they are constructed for the same purpose and therefore have the same capacities. When looking at the right and left hands no structural differences are detectable which could account for the complex behaviour called handedness. Due to this, one can deduce that the behavioural differences between the bilateral limbs, represented simply by manual preference, have their origin in the organization of the brain rather than in the structure of the limbs.[1]

The brain is divided into two cerebral hemispheres, the left and the right hemisphere, which are connected by bundles of nerve fibres called commissural pathways. The left hemisphere controls the right side of the body and the right hemisphere the left side. This contralateral control is due to the crossing of motor and sensory pathways within the brain and brainstem, which connect the hands and the brain.[2]

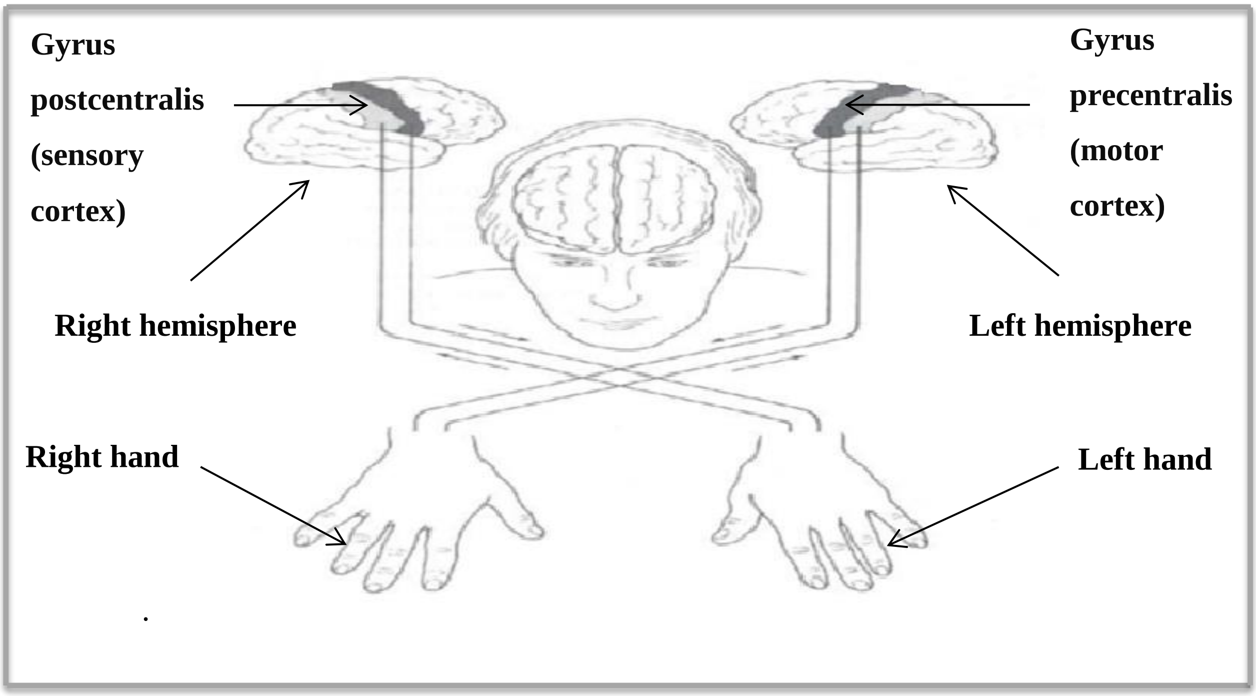

Figure 1: Crossing of motor and sensory pathways. From: Springer & Deutsch (1993)[2]

Consequently, right-handed people have a dominant left hemisphere and left-handed people a dominant right hemisphere, with dominance of one hemisphere determining manual preference.[2] The cerebral dominance is the result of a biological mechanism called lateralization. This process leads to an asymmetrical nervous system which results in a unilateral cerebral control for handedness. In conclusion, handedness depicts a directly observable manifestation of cerebral functional organization.[2]

However, not only motoric functions like handedness are lateralized, other brain functions are also distributed differently between the two hemispheres. Hence, the dominant hemisphere does not only control handedness but is often also responsible for language, in particular speech.[3] On the other hand, the non-dominant hemisphere is considered to be essential in nonverbal thinking like spatial representation, facial recognition and attention.[2,4] Therefore, there have been calls to replace the term "hemispheric dominance" by the term "hemispheric asymmetry" to emphasize the relevance of the non-dominant hemisphere.[2] Springer and Deutsch pointed out that the hemispheric asymmetry is weaker in left-handed individuals than in right-handed ones. This might imply a less significant dominance of the hemispheres, which could account for the increased bilaterality in left-handed people. Nevertheless, even a weak asymmetry of the cerebral hemispheres usually leads to a manual preference. This manual preference, called handedness, describes the tendency to use one hand more skilfully or in preference to the other for single-handed and bimanual tasks.[2]

The best way to measure hand preference is by observing the spontaneous activities of a child.[5] Regarding this type of observation, Oldfield suggested in 1971 to apply a standardized set of items from the repertoire of manual behaviour, which he called the "Edinburgh Handedness Inventory", in order to minimize the variation of items and to facilitate comparison.[6] This inventory includes tasks such as writing, drawing, throwing, scissoring, tooth brushing, cutting and dealing cards. As stated by Fisher, those tasks, which demand great skill, should be observed as they are more strongly lateralized.[7] Therefore, writing and drawing are considered to be especially good indicators of handedness.

1.1.2 Development of handedness

Handedness establishes itself early during development.[2] Already after 31 weeks´ gestation, a left-right asymmetry of the cerebral hemispheres is evident.[8] Apart from these anatomical differences, Michel et al. reported in 1986 the existence of behavioural asymmetries before birth, expressed in terms of thumb-sucking by the fetus possibly as early as 12 weeks of gestational age. Using real-time ultrasound they observed the thumb-sucking of the fetus, which presents an opportunity of assessing handedness before birth. They did not only reveal a distinct bias for sucking the thumb of the right hand but also showed a significant preference for sucking the same thumb, implying consistency throughout pregnancy.[9] After birth this preference is not recognizable anymore, suggesting that the physical maturity required to express this tendency against the forces of gravity has not yet been achieved. However, it has been shown that intrauterine fetal thumb-sucking preferences mostly correlate with head-turning preferences in individuals after birth[9], whereby most newborn favour turning their head to the right side rather than the left.[10,11] Consequently, Largo deduced that the head position acts as an early expression of hemispheric dominance, just like the thumb-sucking, and thus represents another means for investigating lateralization before the establishment of handedness.[12] This assumption is strengthened by Michel´s studies from 1981, in which he observed that the neonatal head orientation preference is a significant predictor of the hand-use preference at the age of 16 to 22 weeks after birth.[13] However, Michel suggested that the head preference is not only related to handedness in terms of lateralization but actually contributes to its development. He proposed that the head preference for the right results in a greater visual experience of the right hand, which precipitates the activation of this hand, as the visual experience is essential for the establishment of hand-eye coordination.[10] These studies illustrate the early beginning of the development of handedness. Furthermore, the studies point out that handedness gradually stabilizes with age; however, there is no general agreement as to what age handedness actually consolidates.

As handedness is part of the fine motor skills, its stabilization depends on the motoric development of the child. This development relies on the maturation of the central nervous system, which is determined by a genetically programmed pattern of behaviour and influenced by environmental stimuli, which may initiate or inhibit such development. Even though motoric reactions mostly occur in a determined chronology after birth, the age of the child at which certain motoric reactions occur can be quite individual.[14] For example, the age at which children start to walk fluctuates between 8 and 20 months.[12] Furthermore, it should be mentioned that there is no consistent order of developmental steps which applies to all children, as motoric development is quite diverse.[12] Focusing on the steps in the development of handedness, it can be observed that the newborn has its hands mostly fisted during the first weeks of life.[15] As soon as physical maturity allows the newborn to overcome the forces of gravity it starts to put his hands into his mouth to investigate them. Within the first 3 months of life the infant begins to hold on to things, firstly as a result of the grasping reflex.[15] While this grasping reflex slowly weakens and finally diminishes at the age of 5-6 months, children begin targeted reaching.[16] This targeted grasping of objects starts at the age of 4-5 months and develops steadily, starting with palmar gripping and resulting ultimately in a pincer grip. At first, infants use both hands to the same extent.[16] A preference in grasping only becomes noticeable at the age of 8 months or older, when children start to use one hand to grip things which are offered to them in the middle, with 9 out of 10 children using their right hand.[12,17] This preference for one hand grows stronger throughout the following years. At the age of 14 months, a distinct handedness in bimanual tasks is often observable[18] and at the age of 18 to 24 months the tendency of hand preference is obvious in most children.[19]

One of the earliest studies investigating the actual consolidation of handedness was performed by Gesell and Ames in 1947. They discovered that bilateral behaviour can still occur after the age of 24 months, and eventually even predominates in children aged 2-3 years. Concluding from these findings, they stated that the sole use of the dominant hand only becomes evident at the age of 4 years. Furthermore, they detected that all of their subjects exhibited a definite unilaterality of the right hand at the age of 5 years, indicating that this age marks a definite stage in the development of handedness.[20] This theory coincides with present beliefs, which state that handedness consolidates at the age of 5 years, implying the establishment of laterality.[16] Further investigations revealed that children, who still use both hands for drawing and writing at the age of 5 to 6 years, have not reached fine-motor skill maturity yet and are often clumsy with both hands.[15] These children should be tested with one of the established tests for handedness like the PTK-LDT, H-D-T or HAPT4-6 to establish their handedness and to support the development of fine motor skills of the preferred hand. Furthermore, it should be emphasized that right-handedness is exhibited earlier during development than left-handedness.[17]

1.1.3 Left-handedness in preterm infants

The World Health Organization defines preterm birth as the delivery of an infant between 20 and 37 weeks of gestation.[21] Furthermore, infant with an extremely low birth weight is defined as one with a birth weight of less than 1,000 grams. There are quite a few studies which investigated the incidence of non-right-handedness in children born preterm, with most studies showing an increased rate of non-right-handedness, especially in the ELBW population. Moreover, ELBW boys have been shown to be more likely to be non-right-handed than ELBW girls.[22]

Already in the seventies non-right-handedness was the subject of several retrospective studies, which primarily focused on the relation between non-right-handedness and perinatal stress.[23-27] Since perinatal stress is common in preterm deliveries, these studies can be applied to the investigation of the association between handedness and preterm birth. In 1971, Bakan studied the relationship between left-handedness and birth order, reporting a higher percentage of left-handed people in the high risk birth order category. He concluded that this increase in left-handedness resulted from a more frequent occurrence of birth stress within this population.[23] In his study in 1973, he investigated this suspected relation between handedness and birth stress more closely. He discovered a significant relationship between the two, with birth stress occurring twice as often among left-handed and ambidextrous children.[24]

In the light of contradictory findings concerning this relationship between left-handedness and birth order,[25-27] the need for prospective studies revealing the relation between perinatal conditions and left-handedness emerged. O'Callaghan et al. were the first to examine the relation between non-right-handedness and perinatal conditions in a prospective study. The results of their study with extremely low birth weight infants supported a correlation. They observed a prevalence of left-handedness of 54% (21 children out of 39) in children with a birth weight lower than 1,000 grams as opposed to a prevalence of 8% (7 out of 87 children) within the population of children with higher birth weights.[28] This distinct tendency of increased left-handedness among ELBW children is supported by the following studies. In October 1987, Ross et al. investigated the hand preference in four-year-old ELBW children and term born infants, with the same distribution of parental handedness in the two groups, finding a significantly decreased frequency of right-handed children in the ELBW cohort. Not only left-handedness was more frequent in the ELBW population but so was mixed handedness.[29] In addition, Marlow et al. detected an increased preference of left-handedness (26.7%) in children born before 31 weeks´ gestation without major neurological impairment,[30] while Saigal et al. in 1992 found a prevalence of 31% of non-right-handedness in their ELBW cohort comprising 114 children aged 8 years.[22] Further supporting this increase, O'Callaghan's study in 1993 showed similar results with a prevalence of non-right-handedness of 34% in 71 ELBW children.[31]

Some more recent studies continue to strengthen this hypothesis of a higher prevalence of left-handedness in children born preterm compared to term born children. Domellöf et al. revealed in their meta-analysis in 2011 that children born preterm have more than a twofold likelihood of being non-right-handed compared to term born infants.[32] One of the latest studies investigating handedness in children born preterm, performed by Johansson et al. in 2014, also showed an increased rate of non-right-handedness in children born before 33 weeks´ gestation.[33] These studies indicate that there is a higher frequency of sinistrality among extremely low birth weight children.

Such an increase in sinistrality has only been observed before in other impaired groups with neurological abnormalities, such as stutterers, epileptics, mental defectives, autistics and in people with reading disabilities.[17,34-37] Even though the origin of this increase in left-handedness in groups with neurological abnormalities, such as prematurely born children, still remains unexplained, most theories about its etiology refer to an increase in non-familial left-handedness.[8,35,38-40] Hereditary left-handedness, which depends on genetic influences, appears not to contribute to this increase in left-handedness in ELBW born. Instead, the special conditions of the early birth have to be considered. The two main theories for this rise in non-right-handedness depict either brain damage or developmental disturbances as the source of this increase among early born children (see below).

1.1.4 Possible sources of an increase in left-handedness in preterm infants

Birth stress is a common complication of preterm birth and can potentially result in cerebral hypoxia. Bakan stated in 1977 that perinatal hypoxia adversely affects the development of the pyramidal system of the left motor cortex, which is more sensitive to anoxia than the right, triggering a neural reorganization. He regarded this neural reorganization as the source of the shift in handedness. Consequently, he classified left-handedness as strictly pathological as it resulted from left hemispheric brain insult.[38]

Studies showing a bias towards left-handedness in uncomplicated pregnancies are questioning this supposition of absolute pathological left-handedness.[9] Taking non-pathological left-handedness into account, Satz postulated in his article in 1972 “pathological left-handedness: an explanatory model” the existence of two types of left-handedness, one being natural and inherited and one being pathological. He considered pathological left-handedness to be the result of “brain injury”, by which he referred to perinatal or neonatal acquired brain damage. Since this brain damage can affect either the right or the left hemisphere, he acknowledged that pathological right-handedness also existed. However, pathological right-handedness appears only rarely, as it is restricted by the lower frequency of natural left-handedness in the population. He also emphasized that such handedness switch, caused by brain damage of one hemisphere,

primarily occurs in populations with perinatal or early postnatal brain injury. Infants have a more plastic nervous system, which allows the contralateral side to assume effective control.[39]
Picking up Satz´s concept of pathological left-handedness, it should be noted that children born preterm are more likely to suffer from such perinatal acquired brain damage than term born infants. This more frequent occurrence of brain lesions, mostly white matter damage, is assumed to be linked to the interruption of the in utero brain development.[41-44] Since the third trimester is characterized by developmental processes comprising growth and differentiation, disturbances during this trimester result in brain lesions, whereby early disturbances provoke white matter damage and late pathogenic events affect the grey matter.[42,45] White matter damage, mostly in the form of intracranial hemorrhage and periventricular lesions, is the major source of brain lesions in children born preterm.[42] It is important to take into account that the left hemisphere is assumed to mature later than the right one.[8] Consequently, it is more vulnerable and more affected by the alterations of early birth than the right hemisphere, implying a greater incidence of brain lesions in the left hemisphere with the potential to interfere with handedness.[46]
Apart from white matter damage, bacterial meningitis is also suspected to affect hand preference by injuring the developing brain.[40,47] Dugdale compared the handedness of children suffering from bacterial meningitis to their healthy sibling in his study in 1981 and found a rise in deviation from right-handedness in those children who had suffered from meningitis. He concluded that brain damage caused by bacterial meningitis has the potential to induce a switch in handedness.[40] Since the incidence of meningitis is higher in preterm neonates compared to term neonates[48], its effect on handedness is therefore more prominent in these children.

However, early birth does not only raise the chance of brain injuries, it also impairs the normal development of the brain and thereby alters its organization. Considering these alterations in organization, Chi et al. proposed that the increase of left-handedness in children born preterm can also be the result of a disturbance in hemisphere development, independent of unilateral brain lesions. As mentioned above, they detected left-right asymmetries in the development of the transverse temporal gyri and the temporal plane, with the right transverse temporal gyrus occurring one to two weeks earlier than the left one.[8] Since these structures only become recognizable after 31 weeks´ gestation, Chi et al. suggested that anatomical asymmetries for left hemispheric dominance are only being established during the last trimester of fetal life and therefore can be altered by preterm birth.[8] Resulting from the delay in maturation, the left hemisphere is, again, more vulnerable to these developmental disturbances. Geschwind et al. share Chi's concept of developmental disturbances: "Changes in the pattern of cerebral control may result from factors operating at different stages of the normal developmental process".[35] Even though they do not neglect Satz's theory, they consider brain damage as an uncommon cause and rather emphasize the significance of the impact of developmental factors on the maturation of the brain. In this context, they stress the effect of pre- and postnatal factors (e.g. testosterone), which modify the direction and the extent in which genetically determined asymmetries, which account for cerebral dominance, are affected.[35] It is important to consider that premature birth may not only alter the stages of the normal developmental process of the brain, but also the factors modifying cerebral dominance.

Witelson und Nowakowski seized on a concept suggested by Geschwind et al. stating that local patterns of the callosal connections can also be altered by intrauterine or postnatal influences. They consider the naturally occurring loss of axons of the corpus callosum to be of strong importance for the development of handedness. Consequently, they describe the increased prevalence of left-handedness in children born prematurely as being a result of their being born prior to the onset of axon loss due to which the development of the corpus callosum is altered.[49]

1.2 Handedness and neonatal morbidities

The prevalence of neonatal diseases increases with decreasing gestational age and decreasing birth weight, indicating that ELBW children are especially at risk of such diseases.[31,50] This is underlined by the fact that up to fifty percent of survivors of less than 750 grams birth weight and the majority of children born at 24 to 25 weeks´ gestation have one or more neonatal complications.[51,52] On top of that, an excess morbidity among extremely preterm boys has been shown compared to girls.[53-55] Since left-handedness also increases with decreasing gestational age[31], an interaction between neonatal diseases and handedness can be suspected. However, there are only few studies relating to this suspected relationship. Most of these studies explore the effect of brain lesions on handedness, since brain lesions occurring early in life can disrupt the development of the nervous system and thereby cause alterations of the functional organization of the CNS.[56]

O'Callaghan et al. showed in their study in 1993 that children with recorded intraventricular hemorrhage of grade 2 or higher have a seven-fold increased likelihood of showing left-handedness, indicating an association between abnormal ultrasound results and left-handedness.[31] Ramadhani et al. confirmed this relation between intraventricular hemorrhage and left-handedness. Moreover, they showed that only children suffering from left-sided IVH were more likely to become left-handed, with right-sided IVH not increasing the chance of left-handedness. While even mild left-sided hemorrhage resulted in an increased chance for left-handedness, no relation between PVL and left-handedness was detectable.[57] Challenging these results, the study of Marlow et al. showed no relation between side or extent of hemorrhage and handedness. The children with abnormal ultrasound and those with a normal one showed the same distribution of hand preference, indicating that major abnormalities detectable by ultrasound do not account for the effect on laterality. Thus Marlow et al. raised the question if minor abnormalities, which are not detectable by imaging, may be the source of the observed excess of left-handedness in the ELBW cohort.[30]

Further investigations concerning the association between non-right-handedness and neurological disorders have been undertaken by Saigal et al. in 1992, in which they discovered that ELBW children with neurological impairment had a significantly higher chance of showing left-handedness.[22] These results correlate with prior assumptions about an increased appearance of left-handedness in “brain injured” populations and suggest comorbidity, even if not detectable by imaging, as a possible source of left-handedness.[39]

1.3 Handedness and cognition

Several studies have investigated a relation between left-handedness and cognition. As reported by Bishop, most studies revealed no link between handedness and intellectual abilities.[34] Despite such rare evidence, a connection between left-handedness and intellectual deficits is still suspected. This might be due to the fact that in groups of mentally retarded, the frequency of non-right-handedness has been shown to be higher.[17,37] Trying to explain this connection, one might suggest brain injury, which not only causes the mental retardation but might also lead to a switch of handedness. However, it is important to acknowledge that these findings cannot be extrapolated to the general population outside of a clinical setting.[2,34] Newcombe’s study from 1973 underlines this by showing that unselected groups of left-handers in the normal population perform just as well as right-handed ones on standard cognitive tasks.[58] This is further underpinned by the fact that some of the most gifted personalities have been left-handed, like Carl Philipp Emanuel Bach, Ludwig van Beethoven, Albert Einstein, Pablo Picasso, Franz Kafka, Johann Wolfgang von Goethe and Leonardo da Vinci.[59]

When looking at ELBW preterm infants, one has to take into account that these children are at a greater risk of suffering from cognitive deficits than term born infants,[50,53,60-64] with male ELBW infants showing even greater rates of cognitive impairment than ELBW girls.[53,65] Moreover, ELBW infants also show an increased frequency of non-right-handedness, just like other mentally retarded groups. Therefore, speculations arose about a relation between cognition and handedness in this population. However, there are only a few studies covering this topic. Ross et al. investigated the suspected relation in 1987, finding an association between the preference of non-right-handedness in children born preterm and a reduced IQ, a delay in language development and difficulties with pronounciation.[29] O'Callaghan's study in 1993 showed a lowered IQ in left-handed ELBW children aged 4 to 6 years, which was not statistically significant though.[31] Studies, like the one of Ross et al.[29], which support association, try to explain this linkage by referring to brain injury, just like the studies examining handedness in other groups of mentally retarded.[66] They consider the linkage to result from a mild form of unilateral brain-injury, which renders the contralateral hand clumsy and lowers cognitive abilities without causing severe neurological impairment.[66]

Saigal's study from 1992 challenges these results as it shows no correlation between handedness and cognitive deficits. Even though Saigal observed decreased cognitive skills within the ELBW cohort compared to the control group, there were no significant differences between left- and right-handed children in terms of school achievements, cognitive function or prevalence of learning disabilities in the ELBW cohort.[22] Similarly, Luciana et al. failed to relate handedness to cognitive performance in ELBW and VLBW children aged 7 to 9 years.[67] Due to these contradictory study results, further investigation will be needed to detect if an association between handedness and cognition exists.

1.4 Former extremely preterm infants at the age of five years

The evolution of modern neonatal intensive care has resulted in a substantially changed ELBW infant population, with an increased chance of survival for those born at the edge of viability and a decrease in morbidity.[21,68] However, the neurodevelopmental outcome remains poor with high rates of cognitive deficits.[63] A number of cohort studies have documented this increased risk of developmental abnormalities in very preterm children.[50,52,53,60-64] ELBW infants are especially at risk of suffering from such developmental abnormalities, as the neurodevelopmental outcome has been shown to worsen with decreasing gestational age.[69,70] The spectrum of these developmental abnormalities is wide and represented by cerebral palsy (CP), neurosensory impairment, including visual and hearing impairment, cognitive deficits and neurobehavioral impairment, such as hyperactivity, attention disorders, emotional problems and peer relationship problems.[41,61,70]

Marlow et al. compared these different domains of neurodevelopmental impairment in an ELBW cohort, determining that cognitive deficits depict the most common disability in these earliest born.[53] Focusing on cognitive disabilities, Taylor et al. investigated the cognitive performance in an ELBW cohort at kindergarten age, detecting a poorer performance in achievement tests and worse learning progress in preterm infants compared to term born control children.[64] This increase in learning disabilities, which has been demonstrated in various other studies as well, is likely to result in difficulties at school and poorer educational achievements.[60,61,64,71] In order to improve the educational achievements of these children, extensive monitoring both prior to and during the first years of school is needed to identify special educational needs and to initiate help.[64] This identification has become especially relevant as more extremely preterm infants are reaching school age nowadays due to the improvements in neonatal medicine.

The aftercare of ELBW children in social pediatric centers constitutes the basis for this identification. In these centers preterm children are re-examined during their first years of life in order to classify and tackle possible foibles and problems. Moreover, at the age of five the cognitive abilities are tested by means of the K-ABC or similar intelligence tests. This intelligence testing helps to classify cognitive deficits more precisely. Likewise, annual preschool examinations help to single out such children with special educational needs. These examinations are performed by the Berlin Senate Department of Health and Social Services and have to be undergone by all children, preterm and term born, in the winter before they are scheduled to start school (for further details see 2.3).

1.5 Aim of the study

When looking at the data dealing with handedness of extremely preterm children, it became evident that not many studies have covered this topic so far. Consequently, there are still many uncertainties about the prevalence of right- and non-right-handedness in these preterm infants. Early studies, like the one of O´Callaghan et al. from 1987, detected a significant increase in non-right-handedness in ELBW children.[22,28-31] However, all these studies were performed prior to the introduction of modern perinatal treatment, including the introduction of antenatal steroids and surfactant, which resulted in a decrease not only in mortality but also in morbidity of extremely preterm children.[21,68] There are only very few studies focusing on the contemporary ELBW population.[32,33] Addressing this shortage of information, the aim of this retrospective study was to investigate handedness and its correlations in a contemporary ELBW population. The main goal was to reexamine the hypothesis of an increased prevalence of left-handedness in “extremely low birth weight” (ELBW) children and to compare the present data to prior study results.

For this purpose, a local ELBW cohort was investigated. The cohort comprised 229 children born in the neonatology department of the Charité University Medical Center, Campus Virchow Klinikum, during the period from 2004 to 2007. The data on handedness was contrasted with the data of a contemporary comparison group comprising 157 ELBW children and 47,524 children with a birth weight greater than 2,500 grams. The data of this comparison group was provided by the Berlin Senate Department of Health and Social Services. Additionally, the data of the study cohort was contrasted with the data of O´Callaghan from 1987.

Since the data of the study cohort included information on neonatal morbidities and information on the intellectual abilities of the children, the suspected association between handedness and neonatal morbidities as well as the controversial link between handedness and cognitive deficits could be investigated. These correlations might help to get a better insight into potential sources of left-handedness and confounding influences in the development of handedness.

2 Methods

2.1 Data privacy and ethics

The ethics review committee of the Charité has approved this study (EA2/015/13). The recording and retention of the data have been authorized by the Charité's commissionaire for data privacy.

2.2 Study cohort

The data of the study cohort was obtained from medical records. Information about handedness, intellectual abilities and neonatal morbidities was gathered by reviewing files. In the case of missing data on handedness, the parents were contacted and interviewed. If information about the medical condition was missing, the neonatal medical records of the child were consulted. Moreover, other social pediatric centers were contacted in order to gain access to the results of intelligence tests of children who had moved or changed their aftercare center within Berlin.

2.2.1 Study population

A total number of 284 ELBW children were admitted to the neonatal intensive care unit of the Charité University Medical Center, Campus Virchow Klinkum, during the enrolment period from 2004 to 2007. Out of these 284 neonates, 55 preterm children died during the stay in the neonatal care unit or after discharge, resulting in a surviving ELBW cohort comprising 229 ELBW children. The data of these 229 participants, who had been recruited through medical records of the Charité, has been evaluated retrospectively. Since the prematurely born children have been continuously looked after and accompanied in their development at the "Centre of Social Paediatrics (SPZ) for chronically ill children and adolescents, department of Neuropaediatrics, Neonatology and Developmental Neurology" of the Charité, a variety of data was available. Of the 229 surviving children all preterm individuals who were at least 5 years old on the 1st of January 2013 and who met the inclusion criteria were included (figure 2).

31 children were excluded because of missing data, with 18 patients not showing up for aftercare and 13 patients having moved away. Despite further efforts to contact these patients or the current social pediatric centers, no data on handedness or cognitive abilities could be ascertained, mostly due to invalid phone numbers.

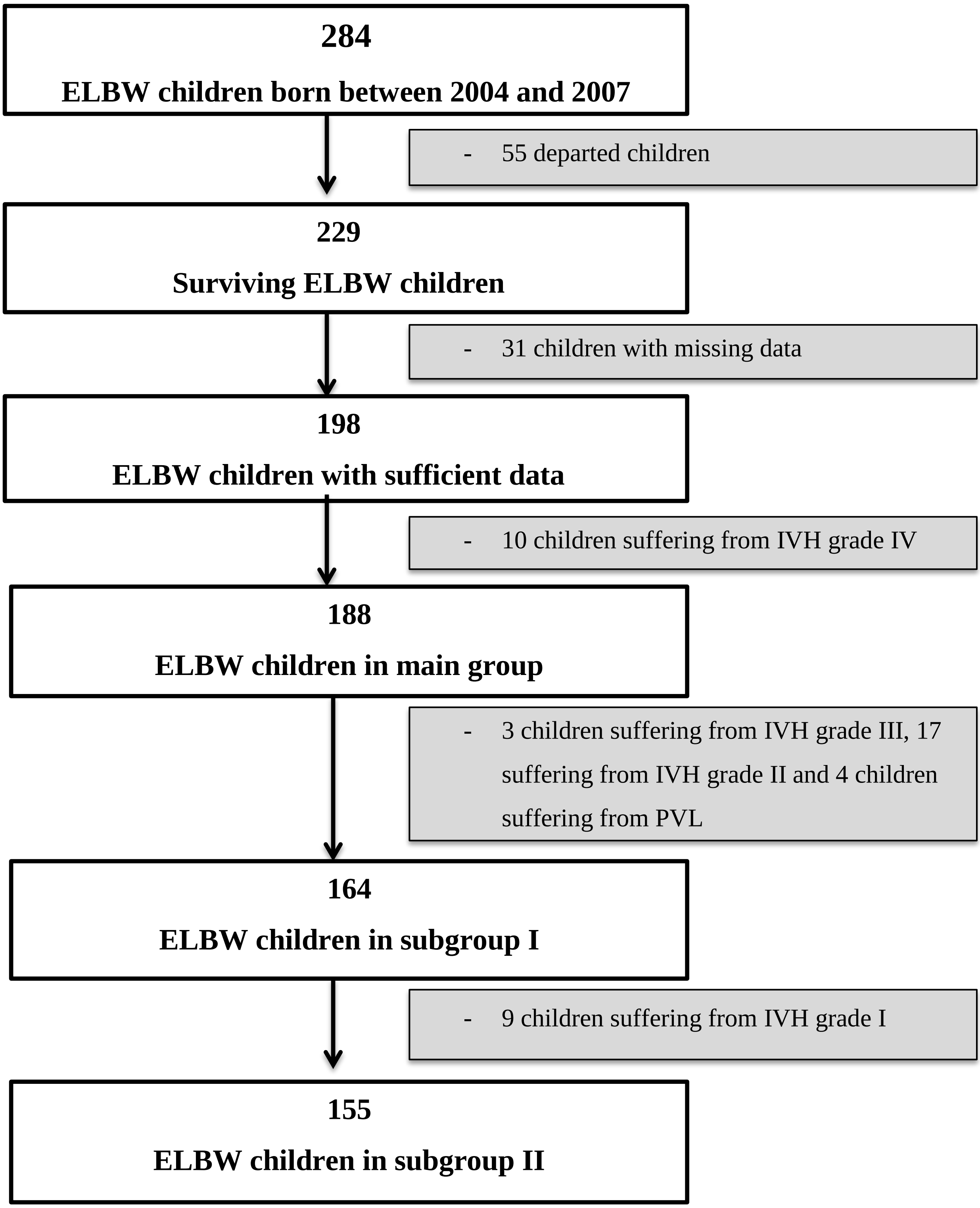

Figure 2: Study population and graduation of groups

10 ELBW infants were excluded based on the presence of exclusion criteria. Strict a priori exclusion criteria included IVH grade IV and the need of a ventriculoperitoneal shunt. Hemorrhage and other conditions, which require treatment using a ventriculoperitoneal shunt, often manifest asymmetrically. This asymmetry potentially influences the process of lateralization due to the greater effect on one hemisphere. Since low and middle grade intraventricular hemorrhages (IVH grade II/III) do not affect the parenchyma in an asymmetrical fashion, children suffering from IVH grade II or III were included in the main group. To reduce possible influences of other neurological disorders, a subgroup was created, which only comprised children without any neurological affection. For this subgroup, a priori exclusion criteria were extended, also excluding children suffering from PVL, IVH grade II and III or from a hydrocephalus. In order to completely eliminate the chance of neurological conditions interfering with the development of handedness, a second subgroup was created, which only comprised children with a normal ultrasound and hence did not even include children suffering from intraventricular hemorrhage grade I.

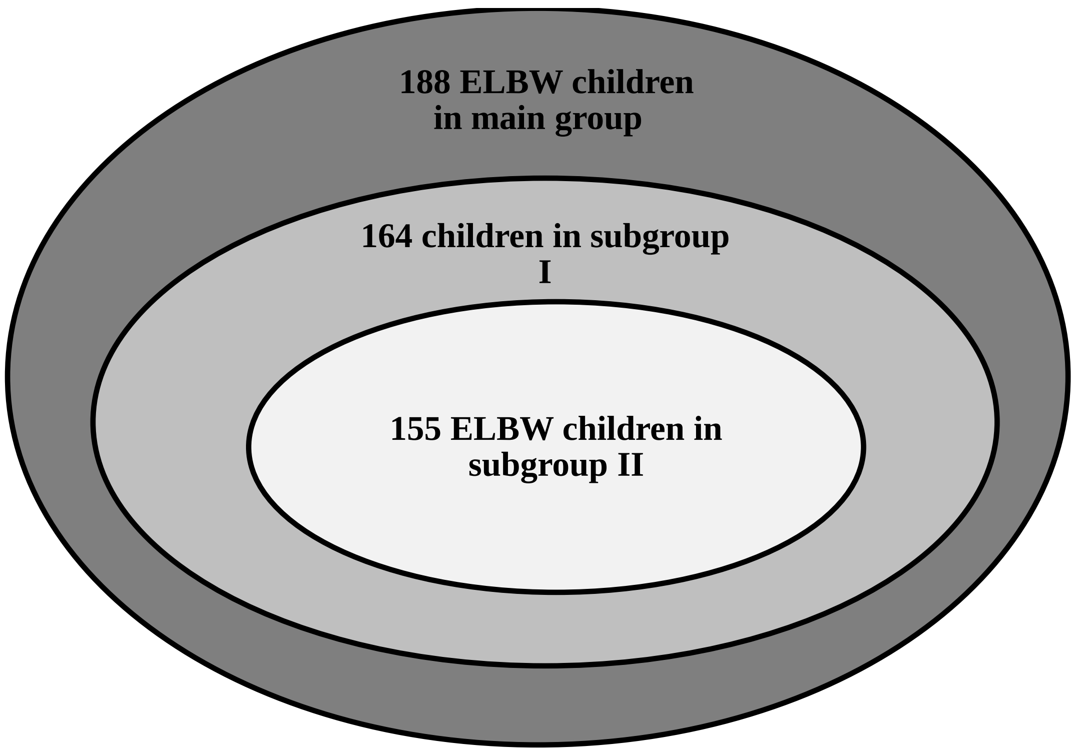

Figure 3: Study groups

The resulting main group comprised 188 ELBW children with a mean gestational age of 26 weeks of pregnancy and a mean birth weight of 780 grams. The 164 children of subgroup I had a mean gestational age of 26 weeks of pregnancy and a mean birth weight of 779 grams and the 155 children of subgroup II a mean gestational age of 26 weeks of pregnancy and a mean birth weight of 780 grams.

Concerning statistical analysis, subgroup I was the major group used for investigation, while the main group and subgroup II were used for comparison. By comparing the three study groups (main group, subgroup I, subgroup II), the effect of the different distribution of neonatal morbidities on the occurrence of non-right-handedness might be revealed. While data on hand preference was available for all children included in the study, data on the cognitive abilities was not accessible for all children.

168 children out of the 188 children in the main group were tested by means of the Kaufmann-Assessment-Battery, 6 children were tested with a different intelligence test, and the remaining 14 children were missing intelligence testing entirely. Concerning the 168 children who were tested with the K-ABC, 7 children were not able to complete the test, resulting in 161 children with a completed K-ABC.
Looking at subgroup I, 146 children out of the 164 completed the K-ABC. The remaining 18 children can be divided into those children who did not finish the K-ABC (3 children), children who were tested with a different test instrument (3 children) and children on whom no intelligence testing data was available (12 children).
In subgroup II, 137 children out of the 155 completed the K-ABC. The 18 excepted children showed the same distribution of exclusion criteria as in subgroup I.

Since most of the children were tested by means of the K-ABC, this group formed the major unit for investigation, with all children without actual test values being excluded.

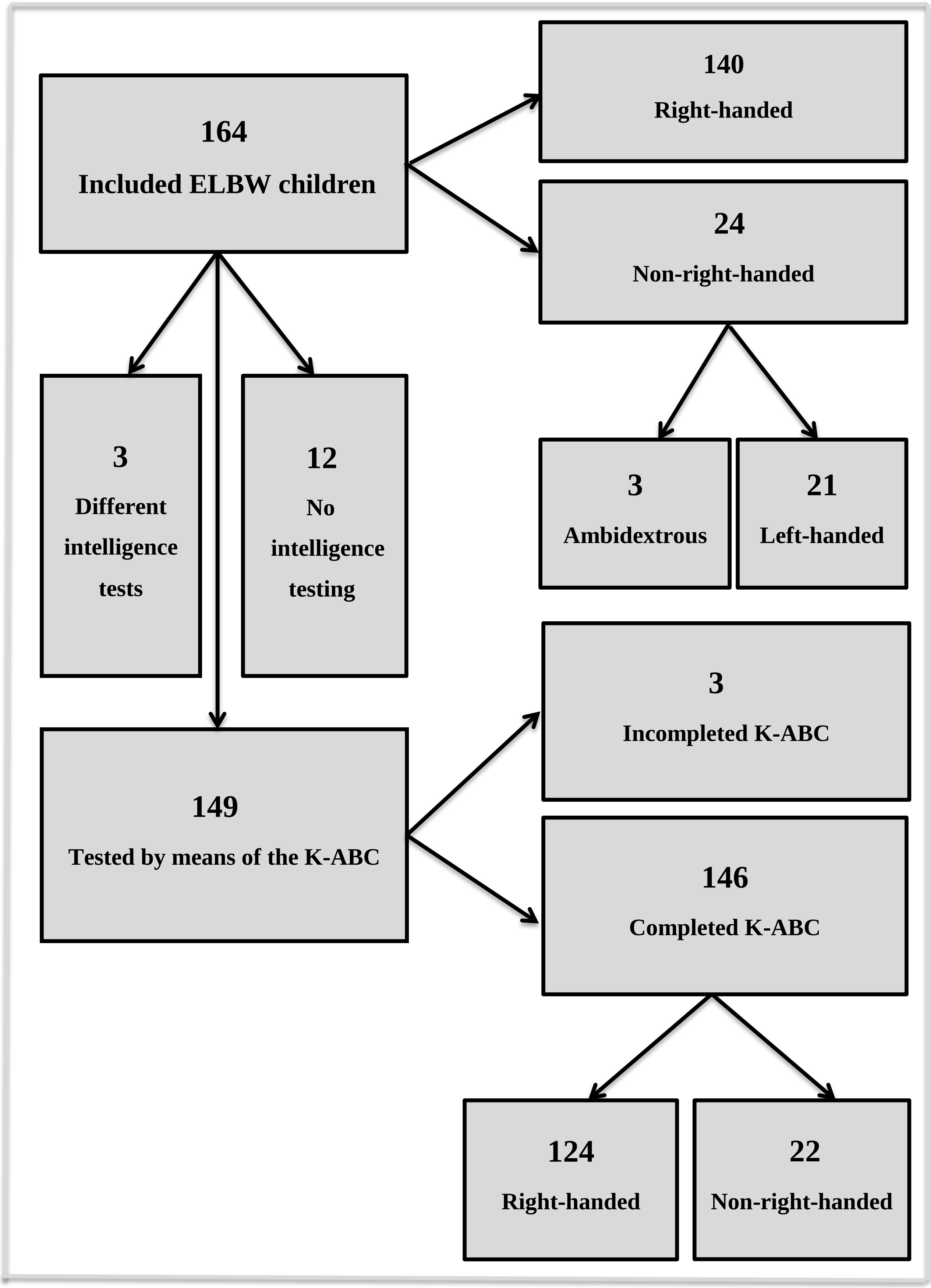

Figure 4: Composition of subgroup I

2.2.2 Handedness tests

All ELBW infants, who are born in the neonatology department of the Charité University Medical Center and who are looked after in the social pediatric center, are tested for handedness at the adjusted age of 5 ¼ years (based on the due date) during their follow-up examinations. This assessment consists of a history taken from the parents and a neurological investigation based on a modified version of the Edinburgh Handedness Inventory. The parents are asked to give information about the usage of the dominant hand of their child during everyday life. Furthermore, they are asked which hand the child uses for activities like drawing, eating, cutting, combing, brushing teeth and buttering bread. During the following examination the children are asked to draw, play ball and to perform a series of hand moves or similar things. Using the verbal and observed information, the hand preference of the child is determined and registered in the medical history, with drawing being considered most important. The term preference is used to describe the observed favouring of one hand over the other when given a choice. If this preference is consistent in most activities, one may assume an established dominance. In contrast, some children use both hands equally skilfully, not showing any preference. These children are to be classified as ambidextrous. However, if a child does not show a distinct hand preference and is clumsy with both hands, further testing is needed. In this case, established handedness tests like the PTK-LDT, H-D-T or HAPT4-6 are applied.

For the surviving 229 ELBW children born between 2004 and 2007, the data on handedness was obtained from the medical records. However, 55 out of the 229 children were not tested for handedness and therefore no information about their handedness was available in the medical records. To gain information about the handedness of these children, their parents were contacted and queried. These children are missing hands-on examination and their handedness has only been gathered by means of anamnesis. None of the children in this cohort was further tested with one of the established handedness tests.

2.2.3 Neonatal morbidities

Neonatal care was rendered according to established national guidelines. The morbidities were classified by the neonatologist responsible for the clinical management of the newborn and entered into the patient´s medical record. The data on neonatal morbidities needed for this study was obtained from the medical records of the children. The focus was placed on medical conditions considered to reflect major complications of extreme prematurity and thought to be associated with alterations of neurodevelopmental outcome or assumed to portray a potential source of left-handedness. Therefore, information about sepsis (defined as clinical signs of infection with a positive blood culture), severe bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), periventricular leukomalacia (PVL), intraventricular hemorrhage (IVH), hydrocephalus, microcephaly (occipitofrontal circumference below the 3rd percentile), hypotrophy (birth weight < 10th percentile), meningitis and infections (i.e. cytomegalovirus) was gathered. In this study, severe BPD was defined as the need for supplemental oxygen at discharge.

Routine cranial ultrasonographic evaluations are performed carefully to a similar schedule on all ELBW children treated at the Charité University Medical Center. The initial evaluation is performed on the first day of life; subsequent evaluations follow routinely on days 3 and 10 and before hospital discharge. More frequent ultrasounds are performed only if needed, e.g. in case of convulsions. The abnormal ultrasound scan findings are classified by degree of abnormality and side. The Papile classification scheme is applied for grading of intraventricular hemorrhage.[72] The stage of intraventricular hemorrhage noted in the medical reports represents the maximum grade detected on cranial ultrasound before discharge.

In this study, every child that showed at least one abnormal ultrasound scan during the first 10 days of its life, no matter whether during the initial evaluation or later on, was allocated to the group of children with abnormal ultrasound.

2.2.4 Intelligence testing

To determine the cognitive abilities of the former ELBW children the "Kaufman Assessment Battery for Children" was used, an individually administered test, that can be applied to children aged 2 ½ to 12 ½.[73] The children in this study were tested before school enrolment at the corrected age of 5 ¼ years. Since this test suits not only healthy, normally developing children, but can also be used for testing children with a lack of concentration, children with insufficient German language skills and even disabled ones[73], it is the basic assessment tool used in the Neuropediatric department of the Charité University Medical Center, Campus Virchow Klinikum.

The original version of the test was developed by two Americans, Alan S. Kaufman and Nadeen L. Kaufman, and was published in 1983 as a tool to estimate cognitive abilities.[74] The German version of the test was first published in 1991 by P. Melchers und U. Preuß.[75] The following details on the test in this paragraph are based on the "Introduction to the Kaufman Assessment Battery for Children (K-ABC) for pediatric neuroclinicians" by Kaufman et al. The test uses standard scores that have a mean set at 100 and a standard deviation of 15. Therefore, the normal range of intelligence ranges from 85 to 115 and all scores below 70, which correspond to the range within the second standard deviation, indicate mental retardation. The test takes approximately 45-60 minutes and consists of 16 subtests. Not all subtests are used during the test, but are chosen depending on the age of the child. The youngest ones have to take up to 7 subtests, while for the older ones (7 years and older) as many as 13 subtests are available. The subtests belong to two different scales; intelligence and achievement. The Mental Processing Scale investigates the problem-solving abilities of the child, interpreted by Kaufman as intelligence, with respect to two different mental processing categories. The Sequential Processing Scale deals with the processing of stimuli with a temporal relationship. The child is required to solve problems in a serial, stepwise manner as stimuli are presented in a sequential fashion. The Simultaneous Processing Scale on the other hand requires the integration of many stimuli at the same time in order to solve the problem. The subtests address visual processing as well as spatial integration of stimuli. Since academic achievement relies on these two processing scores, the sum of these two scales presents an important global measure of intelligence: “The Mental Processing Composite is a unification of the Sequential and Simultaneous Processing Scales and is intended as a measure of total intelligence in the assessment battery”.[73] As mentioned before, the test also comprises an Achievement Scale. This scale measures acquired knowledge (factual knowledge) and application of skills. It is a good way of determining the effectiveness with which a child applies his or her acquired knowledge and is used to check if there is need for support.[73]

In this study the goal was to investigate the cognitive abilities of preterm children rather than the acquired knowledge and therefore the score of the Intelligence Scale (comprising the Sequential Processing Scale and the Simultaneous Processing Scale) was used for statistical analysis. Cognitive impairment was defined as a full scale IQ of less than 70 (2 SD below the population mean). For all scores below 50 a value of 49 was defined, as the K-ABC cannot measure values lower than 50.

2.3 Comparison group

Every child has to attend a preschool examination in the winter before they are scheduled to start school (Berlin School Law, §55a). These examinations are performed by the Child and Adolescent Health Services of the 12 districts of Berlin with a standardized test instrument called S-ENS 76.[76] The data, which captures an entire birth cohort at the age of five to six years, is then forwarded to and pooled at the Berlin Senate Department of Health and Social Services. The goal of these evaluations is to identify children with special educational needs in order to initiate support. Detailed information about the preschool examinations can be found in the annual report of the Berlin Senate Department of Health and Social Services.

As mentioned above, the Berlin Senate Department of Health and Social Services collects the data of preschool examinations. Since handedness is tested during these examinations, this data pool is suited for the investigation of the association between handedness and birth weight. For this purpose, Dr. Susanne Bettge and Dr. Sylke Oberwoehrmann provided detailed information about the 55,400 children, who attended the preschool examinations in 2011 and 2012 (table 1).

Table 1: Results of preschool examinations

Birth weight		Handedness			Total
		RH	LH	BH	
< 1,000g	Number of children	124	22	11	157
	% within birth weight	79.0	14.0	7.0	100.0
1,000-1,499g	Number of children	231	35	10	276
	% within birth weight	83.7	12.7	3.6	100.0
1,500-2,499g	Number of children	2,461	260	59	2,780
	% within birth weight	88.5	9.4	2.1	100.0
≥ 2,500g	Number of children	43,130	3,748	646	47,524
	% within birth weight	90.8	7.9	1.4	100.0
All birth weights	Number of children	45,946	4,065	726	50,737
	% within birth weight	90.6	8.0	1.4	100.0

The cohort of 55,400 children showed a median age of 5 years and 8 months. 50,737 out of the 55,400 children were tested for handedness during the preschool examination by means of drawing and were classified as right-handed, left-handed or ambidextrous. Children of lower birth weights were significantly more likely to be non-right-handed. The prevalence of non-right-handedness among ELBW infants was the highest with 21%, compared with 9.2% in children with a birth weight greater than 2,500 grams. Furthermore, the data of the preschool examinations demonstrated that boys were more likely to be ambidextrous or left-handed than girls. Since Dr. Susanne Bettge and Dr. Sylke Oberwoehrmann are still analyzing the data, exact numbers on the frequency of non-right-handedness of boys and girls are still pending.
However, this data pool is missing information about the medical conditions and IQ scores of the children. This lack of information prohibited the identification of children suffering from asymmetric brain lesions, which potentially promote the incidence of non-right-handedness. Due to the great sample size, the cohort of the Berlin Senate Department of Health and Social Services is well suited for comparison and was used as a reference group. Moreover, it enabled the comparison of ELBW infants to children with a greater birth weight.

2.4 Statistical analysis

The numerically encoded data was collected and entered into “Microsoft® Office Excel Program” and statistically evaluated using SPSS 22 (Statistical Package for Social Sciences for Windows Release 22.0). Descriptive statistics and inferential statistics, with the focus on statistical hypothesis testing, were performed. Concerning statistical hypothesis testing, a p value of <0.05 was considered statistically significant. All statistical tests were two-sided.
First of all, the data was tested for Gaussian distribution by applying the Kolmogorov-Smirnov test. Since the data did not show Gaussian distribution, non-parametric tests were employed. Depending on the scale of measurement, the Pearson-chi-square test (for categorical variables) or the Mann-Whitney test (for continuous variables) was applied for between-group comparisons. If more than two groups were compared, the Kruskal-Wallis test was applied. With the help of descriptive statistics, graphs and tables were constructed and the various descriptive measures such as averages, measures of variation and percentiles (e.g. quartiles) were calculated.

2.4.1 Prevalence of non-right-handedness

The frequency of non-right-handedness (or more specifically left-handedness and ambidexterity) and right-handedness was determined for the three different study groups using descriptive statistics. For further analysis complementary groups were formed and the chi-square test was applied. In addition, the two groups of right-handed and non-right-handed children of subgroup I were compared in terms of birth weight and gestational age using the Mann-Whitney test and in terms of gender applying the chi-square test to detect potential confounders and differences in gender. Lastly, the prevalence of non-right-handedness was determined for the different years of birth from 2004 to 2007 to investigate possible changes over time.

The stratified data on handedness of the 50,737 children of the reference group was used for comparison. First, the data of the ELBW study cohort of the Charité was compared to the data of the children with a birth weight of less than 1,000 grams (ELBW children) by applying the chi-square test. Following, the ELBW study cohort was compared to the group of children with a birth weight greater than 2500 grams. Finally, the data of the study cohort was also contrasted with the prior study results of O'Callaghan et al. from 1987.

2.4.2 Handedness and neonatal morbidities

In order to investigate the suspected relation between handedness and neonatal morbidities, the frequency of the different medical conditions present in the main ELBW cohort was calculated separately for right-handed and non-right-handed children using descriptive statistics. The data was then utilised to contrast the prevalence of specific neonatal morbidities occurring in right-handed ELBW children and non-right-handed individuals using the chi-square test. Likewise, the frequency of medical conditions in ELBW boys and girl was compared.

2.4.3 Handedness and cognition

Another focus of this study was the investigation of the relation between handedness and cognition. For this purpose, the mean scores of the overall IQ (K-ABC) were calculated for all three study groups of the Charité cohort and also separately for the right- and non-right handed children of these groups. The separately calculated scores for right- and non-right-handed children were contrasted using the Mann-Whitney test. Likewise, the scores of male and female ELBW children were compared. Finally, the IQ was calculated for the different years of birth and the Kruskal-Wallis-Test was applied with the goal of revealing a trend over the time period.

3 Results

3.1 Prevalence of non-right-handedness

Table 2 presents the distribution of handedness in the 3 study groups of the cohort (main group, subgroup I, subgroup II). For further statistical analysis, the two categories of left-handed and ambidextrous children were considered as one group of non-right-handed children due to the small number of ambidextrous preterm infants.

Table 2: Composition of main group and subgroups

Category	Main group (n=188)		Subgroup I (n=164)		Subgroup II (n=155)	
	n	%	n	%	n	%
Right-handed children	158	84.0	140	85.4	133	85.8
Non-right-handed children	30	16.0	24	14.6	22	14.2
Left-handed children	27	14.4	21	12.8	20	12.9
Ambidextrous children	3	1.6	3	1.8	2	1.3

The prevalence of non-right-handedness within the three different study groups ranges from 14.2% to 16%. The children of subgroup II without neurological impairment showed the lowest frequency of non-right-handedness. The statistical analysis did not show a significant difference between the main group and subgroup II (P=0.18866 in the chi-square test).

Focusing on subgroup I, the right-handed and non-right-handed children were contrasted in terms of birth weight, gestational age and gender to detect confounding influences on handedness (table 3, 4).

Table 3: Birth weight and gestational age of ELBW infants (subgroup I)

Variables	**Handedness**	
Weight (grams)	**NRH (n=24)**	**RH (n=140)**
Median	808	798
25th Percentile	649	656
75th Percentile	915	915
Gestational Age (WOP)	**NRH (n=24)**	**RH (n=140)**
Median	26	26
25th Percentile	25	25
75th Percentile	28	27

There were no differences in the proportion of birth weight and gestational age between the categories of right-handed and non-right-handed children (P=0.957 in the Mann-Whitney test for birth weight, P=0.302 in the Mann-Whitney test for gestational age).

The cross tabulation shows that the group of non-right-handed children included more males (62.5%) than females (37.5%).

Table 4: Distribution of handedness in males and females (subgroup I)

Category		NRH (n=24)	RH (n=140)	Total
Males				
	number	15	53	68
	% within m/f	22.0	78.0	100.0
	% within handedness	62.5	37.9	41.5
Females				
	number	9	87	96
	% within m/f	9.4	90.6	100.0
	% within handedness	37.5	62.1	58.5
Total				
	number	24	140	164
	% within m/f	14.6	85.4	100.0
	% within handedness	100.0	100.0	100.0

Boys were significantly more likely to be non-right-handed than girls (22% versus 9.4%, P=0.027 in the chi-square test). Confounding influences of birth weight or gestational age were ruled out, as both variables were equally distributed in male and female preterm children.
Statistical testing of the main group and subgroup II confirmed an equal distribution of gestational age and birth weight in right- and non-right-handed children and a raised frequency of non-right-handedness in males.

The prevalence of non-right-handedness in subsequent years of birth was analyzed to look for a trend over time (figure 5).

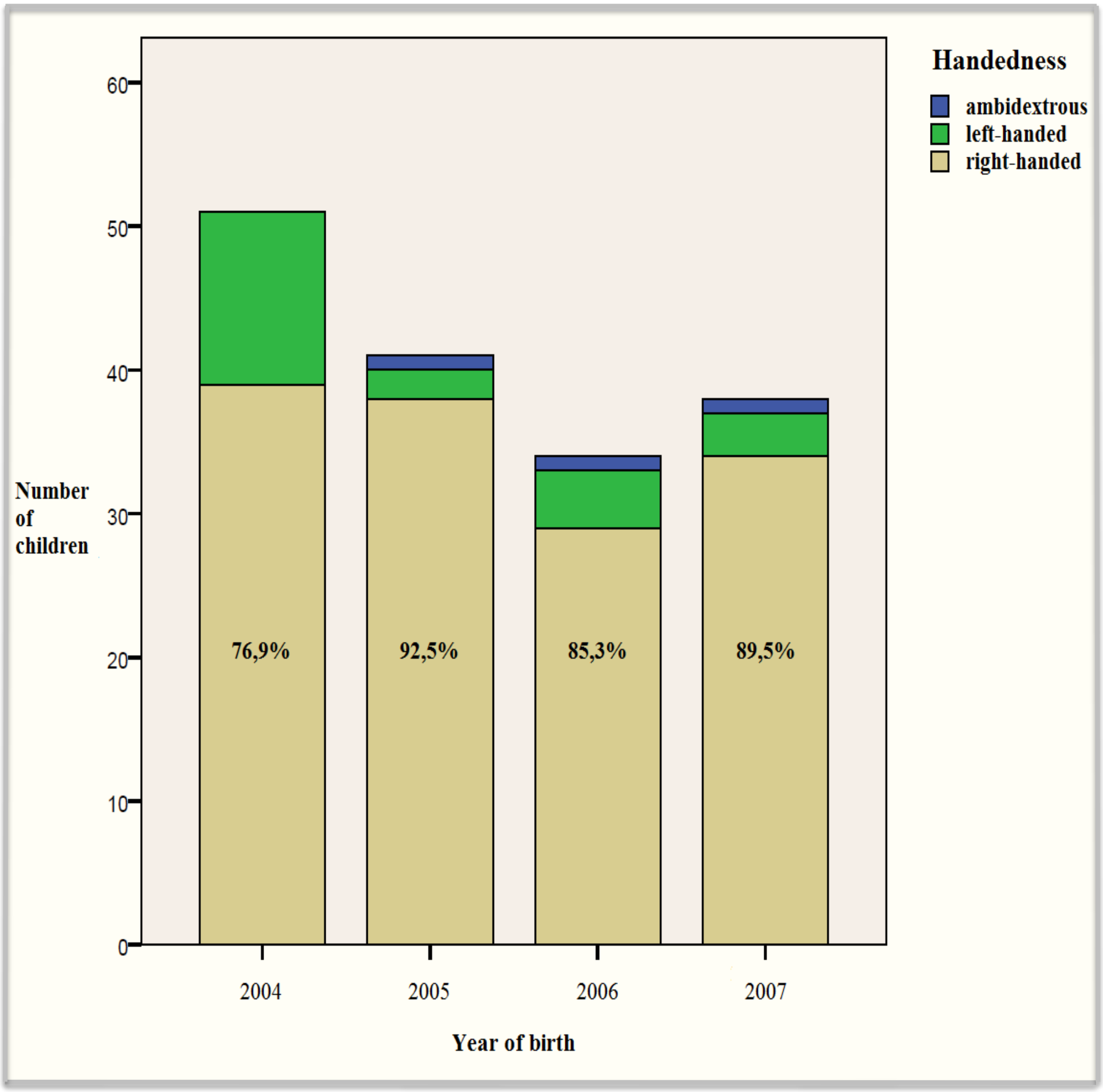

Figure 5: Changes in handedness from 2004-2007 (subgroup I)

As shown in figure 5, the frequency of non-right-handedness varied significantly within the different years of birth (from 7.5% up to 23.1%). It seems to be distributed randomly so that no trend over the time period could be deduced. It should be mentioned that 2004, the year of birth with the greatest number of ELBW infants, showed the highest prevalence of non-right-handedness (23.1%). In contrast, the group of children born in 2005 was not only the smallest group of children, but it also showed the lowest rate of non-right-handedness (7.5%).

3.1.1 Comparison of data

In the following, the data on handedness of the contemporary, local ELBW study cohort was contrasted with the data of the preschool examinations and the data of the O´Callaghan cohort.

Table 5 shows a comparison of the handedness of the ELBW study cohort and the reference group of the Berlin Senate Department. For further information on the cohort of the Berlin Senate Department see 2.3.

Table 5: Study cohort versus comparison group

Data		**Right-handedness**		**Non-right-handedness**		**Left-handedness**		**Ambi-Dexterity**	
		n	%	n	%	n	%	n	%
Study group (Charité data)	Main group	158	84.0	30	16.0	27	14.4	3	1.6
	Sub-group I	140	85.4	24	14.6	21	12.8	3	1.8
	Sub-group II	133	85.8	22	14.2	20	12.9	2	1.3
Comparison group (data of preschool examinations)	< 1000g	124	79.0	33	21.0	22	14.0	11	7.0
	> 2500g	43130	90.8	4394	9.2	3748	7.9	646	1.4

Since the data of the Berlin Senate Department of Health and Social Services included children suffering from neurological impairment and other neonatal morbidities, it was contrasted with the main group of the study cohort for statistical analysis.

No statistically significant differences were noted in the prevalence of non-right-handedness among the ELBW infants of the study cohort or the comparison group (16% versus 21%, P=0.2633 in the chi-square test). Likewise, the ELBW children of subgroup II (with a normal ultrasound) were also no more likely to be non-right-handed than their ELBW counterparts in the comparison group (P= 0.137 in the chi-square test).
In contrast, the ELBW infants of the study cohort were significantly more likely to be non-right-handed than the children with a birth weight greater than 2,500 grams (P=0.0024 in the chi-square test).

In order to assess whether this increase in non-right-handedness in ELBW children is comparable to the one in 1987, the data of the ELBW study cohort was contrasted to the data on non-right-handedness detected by O´Callaghan et al. in 1987. The chi-square test revealed a distinct difference from these prior findings (table 6).

Table 6: Study cohort versus O´Callaghan´s cohort

ELBW Cohort	Number of Children		P-Value
	RH	NRH	
Study cohort (data from the Charité)	158	30	**0.0029**
O'Callaghan's cohort (1987)	39	21	

3.2 Handedness and neonatal morbidities

The investigation of neonatal morbidities of the 188 children included in the main group showed the following results: 47 of the children in the study population suffered from hypotrophy, 32 from BPD, 12 from microcephaly, 31 from sepsis, 3 from meningitis, 10 from NEC, 5 from PVL and 29 from IVH grade I to III.

When looking at the data on neonatal morbidities, it has to be considered that many of the ELBW infants had more than one morbidity, which resulted in multiple inclusions within the different categories of morbidities.

In order to examine the influence of neonatal morbidities on handedness, the occurrence of the various medical conditions in right-handed and non-right-handed children was contrasted. This comparison was performed for the main group, subgroup I and subgroup II (table 7, 8, 9).

Table 7: Neonatal morbidities and handedness (main group)

Neonatal morbidities	Number of affected children (main group)			
	NRH (n=30)		RH (n=158)	
	n	%	n	%
Hypotrophy	11	36.7	36	22.8
BPD	8	26.7	24	15.2
Microcephaly	4	13.3	8	5.1
Infection	21	70.0	86	54.4
Sepsis	5	16.7	26	16.5
Meningitis	0	0.0	3	1.9
NEC	3	10.0	7	4.4
PVL	2	6.7	3	1.9
IVH I-III	6	20.0	23	14.6
Hydrocephalus	0	0.0	2	1.3

Table 8: Neonatal morbidities and handedness (subgroup I)

Neonatal morbidities	Number of affected children (subgroup I)			
	NRH (n=24)		RH (n=140)	
	n	%	n	%
Hypotrophy	10	41.7	35	25.0
BPD	7	29.2	21	15.0
Microcephaly	3	12.5	7	5.0
Infection	18	75.0	72	51.4
Sepsis	4	16.7	21	15.0
Meningitis	0	0.0	3	2.1
NEC	2	8.3	5	3.6
IVH I	2	8.3	7	5.0

Table 9: Neonatal morbidities and handedness (subgroup II)

Neonatal morbidities	Number of affected children (subgroup II)			
	NRH (n=22)		RH (n=133)	
	n	%	n	%
Hypotrophy	9	40.9	34	25.6
BPD	5	22.7	19	14.3
Microcephaly	3	13.6	7	5.3
Infection	16	72.7	68	51.1
Sepsis	4	18.2	20	15.0
Meningitis	0	0.0	3	2.3
NEC	2	9.1	4	3.0

A chi-square test was performed to examine more precisely the distribution of medical conditions in right-handed and non-right-handed children (table 10). As explained above, the interaction between neonatal morbidities, due to multiple inclusions, could not be avoided. The fact that no child within the group of non-right-handed preterm children suffered from meningitis made statistical analysis for this medical condition impossible. :

Table 10: Significance of differences in neonatal morbidities in right-handed and non-right- handed children (subgroup I)

Neonatal morbidities	P-value	Neonatal morbidities	P-value
Hypotrophy	0.135	NEC	0.272
BPD	0.137	IVH I	0.621
Microcephaly	0.165	Infection	**0.045**
Sepsis	0.765		

Non-right-handed children suffered significantly more from infections than right-handed individuals (P=0.045 in the chi-square test). For all the other neonatal morbidities present in subgroup I, no statistically significant differences were detected.

Statistical analysis comparing the incidence of neonatal morbidities in right-handed and non-right-handed children was also performed for the main group and subgroup II, showing no statistical difference between the two groups. The increase of infections in non-right-handed children detected in subgroup I could not be confirmed in the other two study groups. Furthermore, no differences were observed for the other neonatal morbidities present in the main group (IVH grade II and III, PVL and hydrocephalus) either.

Another focus of this study was the investigation of differences in the incidence of the various neonatal morbidities in male and female ELBW children. Table 11 shows the distribution of neonatal morbidities in ELBW boys and girls.

Table 11: Neonatal morbidities by gender (main group)

Neonatal morbidities	Number of affected children (main group)				P-Value
	ELBW boys (n=82)		ELBW girls (n=106)		
	n	%	n	%	
Hypotrophy	16	19.5	31	29.2	0.174
BPD	17	20.7	15	14.2	0.247
Microcephaly	6	7.3	6	5.7	0.766
Infection	49	59.8	58	54.7	0.553
Sepsis	16	19.5	15	14.2	0.331
Meningitis	1	1.2	2	1.9	1.000
NEC	3	3.7	7	6.6	0.517
PVL	3	3.7	2	1.9	0.655
IVH I-III	17	20.7	12	11.3	0.103
Hydrocephalus	1	1.2	1	0.9	1.000

Even though ELBW boys appear to be more affected by various medical conditions, the chi-square test revealed no significant differences (table 11).

3.3 Handedness and cognition

Looking at the ELBW children who have been successfully tested with the help of the K-ABC, a median of 96 was detected for all three study groups of the ELBW cohort (main group, subgroup I, subgroup II). This value is within the normal limits, but slightly shifted to the left, considering a population average of 100.

In order to detect differences in the intellectual abilities of non-right-handed and right-handed children, both groups were contrasted (see figure 6, table 12).

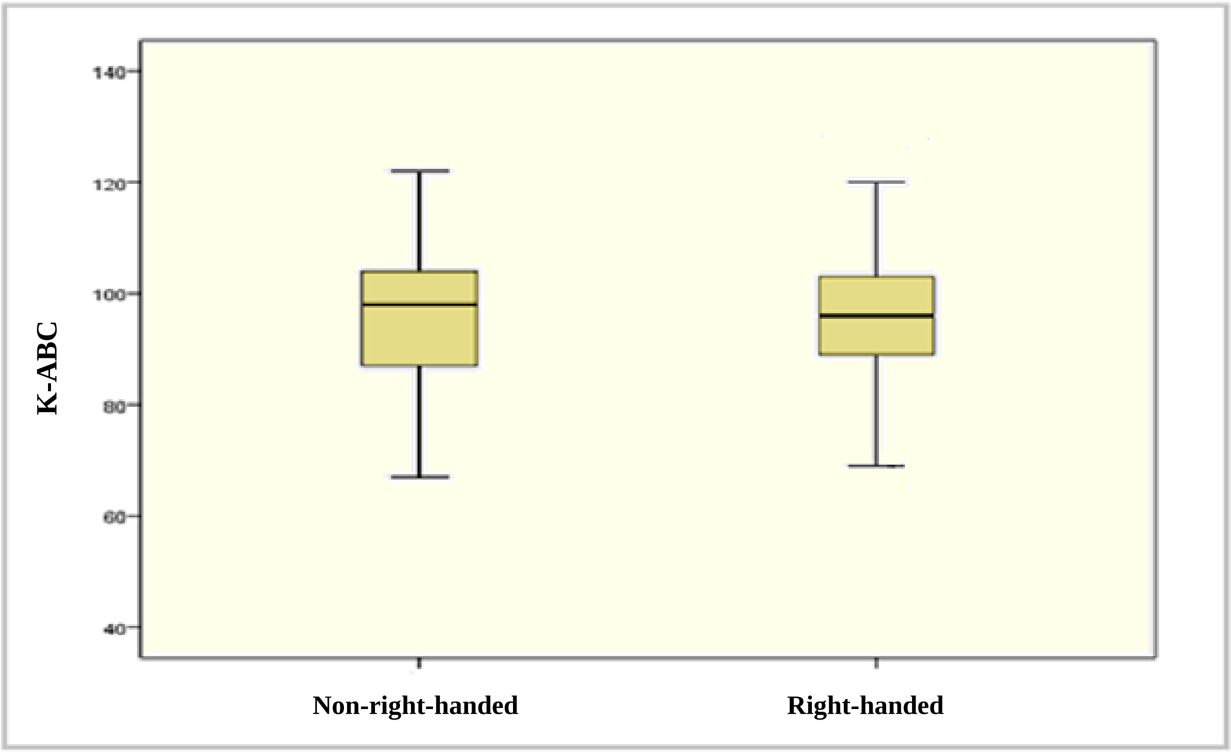

Figure 6: K-ABC scores of right-handed and non-right-handed children (subgroup I)

Cognitive scores did not statistically vary with hand preference in subgroup I (P=0.945 in the Mann-Whitney test). The same result was reached when contrasting the non-right-handed and right-handed children of the main group and subgroup II.

Table 12: K-ABC scores of study groups

K-ABC	ELBW Cohort					
	Main group (n=161)		Subgroup I (n=146)		Subgroup II (n=137)	
	NRH (n=26)	RH (n=135)	NRH (n=22)	RH (n=124)	NRH (n=20)	RH (n=117)
Median	99	96	98	96	99	96
25^{th} Percentile	89	89	87	89	88	89
75^{th} Percentile	104	103	104	103	104	103

The group of non-right-handed children, which comprised 22 individuals, can be further divided into 3 ambidextrous and 19 left-handed children (figure 7).

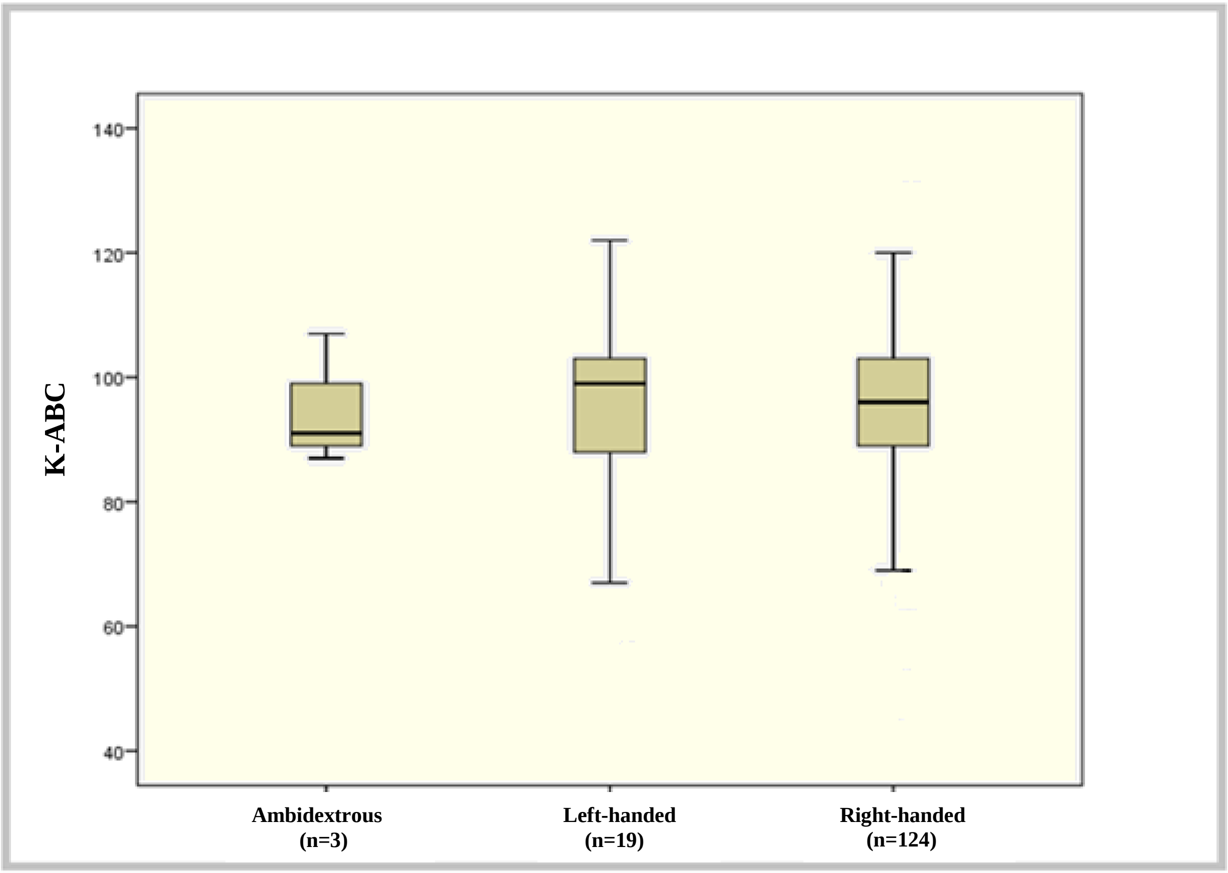

Figure 7: K-ABC and handedness (subgroup I)

These segregated data can be used to compare the cognition of right-handed and left-handed children. The cognitive scores of right-handed and left-handed ELBW children were no different from each other (P=0.398 in the Mann-Whitney test). Considering the group of ambidextrous children, it is of no significance to examine this group more precisely as it only comprised 3 children.

The results of the present study suggest that the hypothesis of no difference in cognitive performance between right-handed and left-handed ELBW children can be accepted as true.

Next, the cognitive scores of female and male ELBW infants were contrasted. No statistically significant difference was found for handedness by gender within subgroup I (P=0.257 in the Mann-Whitney test). Likewise, no difference was detected when performing the same statistical analysis in the main group and in subgroup II.

Additionally, the data of the K-ABC was used to compare the cognitive scores of the different years of birth from 2004 to 2007. Figure 8 shows the distribution of the mean scores of the K-ABC.

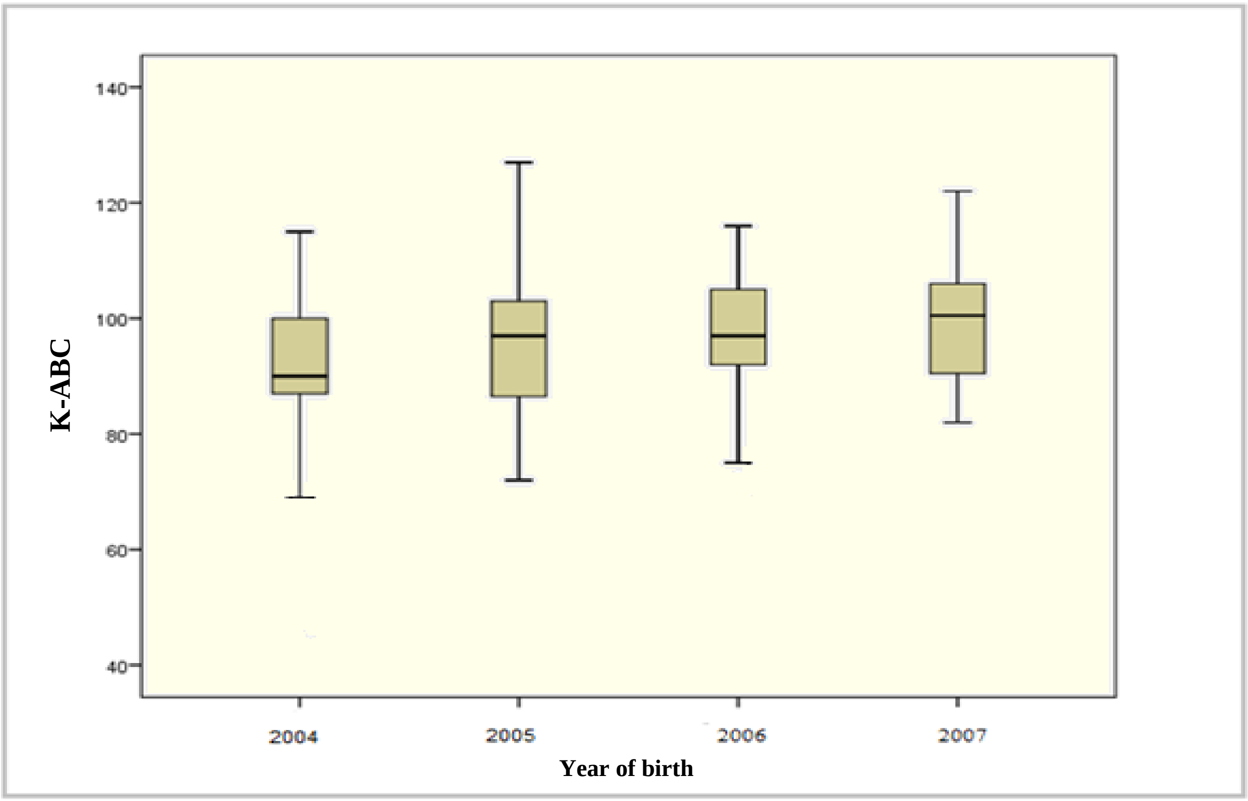

Figure 8: K-ABC scores from 2004-2007 (subgroup I)

Valid cognitive scores were ascertained for 46 children in 2004 (90.2%), for 35 children in 2005 (85.4%), for 33 children in 2006 (97.1%) and for 32 children in 2007 (84.2%). The median varied from 90 in 2004 to 97 in 2005 and 2006, up to 101 in 2007. A statistically significant difference in cognitive scores over time was detected in subgroup I (P=0.032 in the Kruskal-Wallis test). This difference could not be confirmed within the other two study groups (P=0.134 in the Kruskal-Wallis test for the main group, P=0.059 in the Kruskal-Wallis test for subgroup II).

4 Discussion

4.1 Summary of the main results

The contemporary, local ELBW study cohort showed a rise in non-right-handedness, strengthening prior study results which suggested an increase in non-right-handedness in these early born children. The data provided by the Berlin Senate Department of Health and Social Services confirmed this rise in non-right-handedness in former ELBW infants compared to children with a higher birth weight. However, it is important to stress that the detected increase in non-right-handedness was significantly lower compared to the result of O'Callaghan et al. from 1987. This trend towards a lowered incidence of non-right-handedness in ELBW infants became particularly obvious in subgroup II of the ELBW study cohort, in which all children suffering from neurological impairment were excluded. On top of this, a higher rate of non-right-handedness in ELBW boys compared to ELBW girls was detected.

Since the data of the study cohort included information about intellectual abilities and data on neonatal morbidities, this cohort was suited for the investigation of further correlations of handedness. The statistical analysis, performed to detect possible associations, revealed no link between handedness and most neonatal morbidities and no link between handedness and cognition. The only medical condition for which an association was detected was infection, albeit only in subgroup I. For all other neonatal morbidities, no statistically significant differences were noted between right- and non-right-handed children. Likewise, no statistically significant differences in the incidence of medical conditions between male and female ELBW infants were observed. The median overall IQ score for all 3 study groups was within the normal limits. The two categories of right-handed and non-right handed preterm children, just like the two categories of female and male ELBW infants, did not differ in their cognitive scores. Comparing the IQ scores of the different years of birth from 2004 to 2007, a slight increase in the intelligence performance from 2004 to 2007 could be observed. This rise, however, was only noted in subgroup I.

4.2 Strengths and weaknesses of this study

In this study the handedness of ELBW infants and its correlations have been investigated. The data of the contemporary, local ELBW study cohort was obtained from patient´s medical records. The retrospective nature of data collection portrays a major limitation, since one cannot rule out incorrect record keeping, which potentially impairs the data quality. On top of this, the medical records were insufficient in some cases, not containing all information needed. Especially data about the handedness of the children was missing in some records. This is mainly due to the fact that some children were not tested during their follow-up appointments. In order to include these children, nevertheless, the parents were contacted and interviewed. Even though the data might have been more reliable if solely based on medical records, this deficiency was accepted in order to create a cohort of sufficient size. A further limitation arises from the fact that the parents were not questioned about their handedness. Defining the parents' handedness would have made it possible to exclude confounding genetic components. However, since the medical records did not include any information about the handedness of the parents, finding out details on the parents' handedness would have gone beyond the scope of this study. Focusing on the strengths of this study cohort, one has to consider its uniformity. Since all children were born and treated in the same hospital following the same guidelines, perinatal bias was avoided. Nevertheless, the drawback of this setting is the resulting selection bias. It should be emphasized that the cohort only comprised ELBW infants, rather than ELBW and VLBW infants. This is important, as left-handedness increases with decreasing gestational age and with decreasing birth weight.[31] The greatest weakness of this cohort, however, results from the small sample sizes and the missing reference group of children with a greater birth weight. In order to tackle this weakness, a comparison group comprising a greater number of children was consulted. Since the data of this comparison group was collected from preschool examinations, which all children are legally required to undergo, this cohort also included children of greater birth weights, thereby providing a control group of term born children. While on the one hand the standardized testing during the preschool examinations can be considered as an advantage, it also limited the amount of information of the data base. Due to the standardized examination, only specific information was ascertained, e.g. only information about the birth weight was ascertained and not about the gestational age. Resulting from this lack of information about the gestational age, the difference between preterm birth and small for gestational age (SGA) cannot be distinguished. Moreover, the data pool also lacks information about the neonatal morbidity of the children and about the cognitive abilities. For this reason, this data pool is insufficient as to a proper investigation of the relations of handedness. Nevertheless, this cohort was well suited for comparison due to the great number of cases.

However, when comparing the study cohort to the comparison group, it should be taken into account that the two cohorts varied substantially in their composition due to the different methods of data collection. Not only did the inclusion and exclusion criteria of the two cohorts differ, but so did the testing of handedness and the ascertainment of data. On top, the fact that the ELBW children of the contemporary study cohort also underwent the preschool examinations has to be considered. Since the cohort of the Berlin Senate Department of Health and Social Services comprised a much greater number of children, this effect is minor when comparing the ELBW children of the study cohort to the children with a birth weight greater than 2,500 grams. However, when comparing the 188 ELBW children of the study cohort to the 157 ELBW children of the comparison group the multiple inclusions potentially distorted the comparison.

4.3 Evolution of lateral preference

Geschwind and Galaburda described a widespread functional dominance in the animal kingdom, just like in humans, but with a less elaborate pattern of asymmetric function.[35] This functional dominance, depicted by a consistent paw preference in activities, which involve the use of only one hand, has been reported for rats, cats, mice, monkeys, chimpanzees and guerillas.[77-79] Concluding from the results of research, lateralization appears to be a fundamental principle in the organization of the brain and behaviour in all vertebrates, rather than a specific trait of only certain species.[80,81] This common appearance of functional dominance in non-humans just like in human species raised the idea of an evolutionary advantage.[34]
Bishop discussed this adaptive advantage of handedness in his book in 1990 and presented two related hypotheses. The first hypothesis addressed motor learning. In the early stages of motoric development, the performance of a motor skill is rather slow. This is due to the fact that the different muscle groups are still poorly coordinated, which is why the movements need to be monitored closer in terms of feedback mechanisms to enable corrective adjustments. As the movement pattern is learned, a motor program evolves with specified sequences of coordinated movements of different muscles, which enables the execution of a stereotyped, pre-programmed movement without the need of a feedback system. In conclusion, one might expect that the more stereotyped the movement pattern, the more advantageous it would be to concentrate learning on one side. Therefore, handedness should be most apparent in highly skilled, stereotyped, preprogrammed movements. The second hypothesis presented by Bishop may be termed the interference hypothesis. There is some evidence that learning a motor movement with one hand facilitates the performance of mirror-image movements with the other hand.[82] Nevertheless, up to now the basis of this phenomena cannot be explained in terms of neurophysiology and there are controversial opinions about its existence.[34]

Looking at the current overall data on animals and humans, the question whether handedness actually has adaptive advantages for motor learning cannot be answered convincingly.

4.3.1 Bias to right-handedness

Even though lateral preference is evident in human and non-human species, the bias to right-handedness appears to be a specifically human trait. There are some interesting cases of lateral bias in other species as well, e.g. left-footedness in parrots[83], but the only non-human primate for whom a population tendency to right-handedness has been actually claimed is the ape.[79,84,85] Most non-human species rather show an incidence of right- and left-pawedness of approximately 50% each.[3] Annett proposed that this equal distribution within the animal kingdom is based on chance environmental factors, which cause one side to be slightly more proficient than the other. She acknowledged that in humans, chance also plays a substantial role in determining handedness, but is superimposed by the effect of a right shift factor, which gives a selective advantage to the right hand.[86] Considering the population bias in apes, she suggested that chimpanzees show a genetically determined right shift with a less stronger magnitude of expression than in humans.[87]

4.3.2 Theories about the etiology of handedness

There are several theories about the etiology of this disproportionate population dominance in humans.[2] Thomas Carlyle already proposed in the nineteenth century that right-handedness was a consequence of early warfare, as warriors held their shield in the left hand to protect their heart. As a result, the right hand grew more skillful during the millenniums of war and was used more often than the left hand during everyday life.[77] In 1862 the Scottish scientist Buchanan developed another theory to explain the population bias to right-handedness, which holds the position of the internal organs responsible for this preference: "handedness depends upon mechanical laws arising out of the structure of the human body”.[88] These early concepts, however, fail to explain left-handedness.[77]

More modern theories about the etiology of handedness mostly debate the effects of genetic and environmental factors. Chamberlain already investigated in 1928 the inheritance of left-handedness, detecting that the chance of two right-handed parents to have a left-handed child is about 2%. He pointed out that this chance increases to 17% with one left-handed parent and to 46% with both parents being left-handed.[89] This data suggests a genetic influence on the development of handedness. As discussed by Springer and Deutsch, one could also assume that these traits run in families because of an exposure to similar environmental factors and other forms of non-genomic inheritance. Left-handed parents for example might influence the development of handedness by providing a left-handed model for their child to imitate or even just by having a more tolerant attitude towards non-right-handedness.[2] Therefore, both factors have to be taken into account when looking at handedness.

Considering the genetic approach, many different genetic models have been proposed in order to account for the variation in handedness. Left-handedness cannot be explained in terms of the classical Mendelian approach incorporating a recessive allele for left-handedness, since left-handed parents can produce right-handed offspring.[90] Nevertheless, several other single-locus models have been proposed with the one of McManus and the one of Annett being the most famous ones.[3,91] Both models do not propose the existence of a gene encoding for right- and left-handedness, but rather of an allele encoding for right-handedness and one encoding for variable handedness. Since the allele encoding for variable handedness does not induce a preference, the hand preference is determined by chance and not by genetics.[92-94] Consequently, the genetic inheritance only influences whether a bias to right-handedness will be expressed.[92,93] Contrasting these single-locus models, the model of Levy et al. proposes a two-loci, four-allele model, with one locus encoding for cerebral dominance for speech and the other one encoding either for contralateral or ipsilateral hand control relative to the dominant hemisphere.[95] Yeo et al. on the other hand reject these theories about a direct genetic effect on handedness and rather consider a deviation from moderate right-handedness to be the result of early polygenetic homozygosity, which causes developmental instability and thus extreme right- or left-handedness.[96] Lately several large-scale genome-wide studies tried to find a single locus associated with handedness, with none finding a significant correlation.[97,98] Results of these studies suggest that handedness is a polygenic trait, partly controlled by genes, that establishes body asymmetry during development.[99]

However, even though genes appear to have a great impact on handedness, further factors have to be taken into account to explain findings such as the fact that 23% of monozygotic twins, who share the same genes, are of opposite handedness.[100] Some theories even consider handedness to be an exclusively learned behavior independent of genetic influences. Hildreth for example, postulates cultural pressure to be the sole source of the right-handed bias within the population: “People are right- or left-handed because they have learned to be, not because they were born that way”.[34] She describes handedness as a habitual behavior, which is influenced throughout the period of growth and which follows the laws of learning and habit formation just like any other behaviour that results from practice and exercise.[34] Corballis and Beale also hold cultural pressures, particularly the right-handed environment in the human species, accountable for the bias to the right hand since non-human species, which inhabit an environment in which left and right are largely irrelevant, do not show such a bias. This right-handed environment is depicted by social organizations as social customs based on conventional use of one side such as hand shaking.[78] Blau stresses this cultural pressure even more by talking about dextrality being the "cultural law".[101]

All in all, the learning theories, just like the genetic approaches, cannot explain the whole phenomenon of handedness. The major problem of the learning theories is the fact that they cannot explain how the bias towards right-handedness in human cultures originated without referring to biological predispositions.[2] If handedness did not have a genetic source and was solely a consequence of cultural pressure, one would expect historical and geographical variability in its manifestation. But there is no geographical difference in handedness: "No cultural group has been found in which the incidence of left-handedness deviates substantially from 8%".[3] Moreover, it fails to explain the early appearance of lateral preference in infants, which has been linked to later hand preference[12] and which has been shown to be related to parental handedness.[102] Since both theories cannot sufficiently explain the development of handedness, it should rather be considered as the result of a continuous interaction between genetic and environmental influences, with both factors being indispensable for the development and impossible to disentangle due to their interaction in the developmental process.[80]

4.4 Handedness of former ELBW infants

O´Callaghan´s study from 1987 initiated the discussion about an increased rate of non-right-handedness in ELBW children by showing a rate of left-handedness as high as 54% in these early born children. Further studies during the nineties widely supported such an increase in left-handedness with values in the range of 30%. Likewise, the contemporary local ELBW study cohort showed a distinct increase in the incidence of non-right-handedness. The corresponding figures of the comparison group confirmed this increase of non-right-handedness in ELBW infants. At this, the ELBW children of the comparison group showed the highest prevalence of non-right-handedness (21%). This increased rate of non-right-handedness compared to the ELBW cohort of the Charité is due to the fact that children suffering from asymmetric brain lesions, which have the potential to promote the occurrence of left-handedness, were neither identified nor excluded. Hence, the ELBW infants of subgroup II of the Charité cohort showed the lowest rate of non-right-handedness (14.2%) as all children with any kind of neurological affection were excluded. Nevertheless, this variation in the prevalence of non-right-handedness within the two different ELBW cohorts was not significant according to the statistics. In contrast, the data of the study cohort differed significantly from the study results of O'Callaghan et al. in 1987, indicating a decrease in non-right-handedness in extremely preterm infants within the last decades.

The ELBW children of the study cohort were significantly more likely to be non-right-handed than the corresponding term born individuals of the comparison group. The children with a birth weight greater than 2,500 grams only showed a prevalence of approximately 9% of non-right-handedness. This detected prevalence of 9% coincides with older data on left-handedness within the general population. Studies like the one of Porac & Coren, McManus, and Springer & Deutsch described a worldwide prevalence of non-right-handedness of 8%.[1-3] However, the current study data questions the reported increase of left-handedness within the general population over the last decades.[32,103,104] Since the comparison group included as many as 47,524 children with a birth weight greater than 2,500 grams, this data was considered statistically significant and utilised for comparison rather than using the varying data from literature.

As mentioned above, the comparison of the current study data to prior study results revealed that the rate of left-handedness in ELBW survivors has significantly decreased over recent decades. Comparing the study designs of the various studies included in this work, it became evident that most of the studies differ in the use of cut-off for stratifying relevant categories, such as gestational age and birth weight, aggravating the comparison of the study results. The comparison is further complicated by the various definitions of handedness, which vary from definitions treating handedness as a binary categorical variable[3] up to definitions considering handedness as a continuous variable with a spectrum ranging from extreme right-hand preference, through equal preference for both sides to extreme left preference.[34] When contrasting the different study results, one also has to consider the different sizes of the cohorts. It is important that the study cohorts need to be sufficiently large in order to gain statistically relevant results. The study of O´Callaghan et al. from 1987, which initiated the discussion about an increased rate of non-right-handedness in ELBW children, only included a cohort of 39 children.[28] Due to the small cohort size the results can easily be confounded. Therefore, one might argue that the high prevalence of non-right-handedness detected by O´Callaghan et al. is rather a play of chance and statistically not significant. However, subsequent studies in the nineties, which comprised greater cohorts, also showed a significant increase in left-handedness, indicating that a difference in handedness of ELBW infants and term-born children exists. Nevertheless, the rise detected in the nineties was much less significant, with values varying around 30%.[22,29-31]

Apart from the study designs, the effect of the improvements in neonatal medicine over the past couple of years has to be considered in order to explain the reduction in non-right-handedness in extremely preterm infants.

4.5 Impact of improvements in neonatal medicine on neonatal morbidities and handedness

Since the decrease in left-handedness in ELBW children went hand in hand with the improvements of neonatal medicine, it appears reasonable to presume an association between the two. While at first the changes in treatment only led to a reduction in mortality, later a decrease in morbidity was also achieved.[68] This reduction in morbidity is suspected to contribute to the decrease in non-right-handedness in ELBW infants. Major changes in treatment include the introduction of surfactant therapy, an increase in Caesarean sections, application of antenatal steroids, nitric oxide inhalation, and reduction of sepsis, oxygen saturations and of the usage of postnatal glucocorticoids.[21,51,68,105] All these changes resulted in an improved outcome and general health condition of extremely preterm infants, accompanied by a reduction of further medical complications and of harmful influences from neonatal treatment. Consequently, the likelihood of events interfering with handedness has substantially decreased.

Looking more specifically at the effect of particular medical conditions on handedness, a distinct relation has so far only been found for cranial abnormalities and handedness.[31,57] Consequently, special attention should be paid to the changes in neonatal medicine, which have led to a diminution of adverse events. In this context, one has to consider the introduction of antenatal steroids. Antenatal steroids have been shown to significantly lower the rate of periventricular leukomalacia and intraventricular hemorrhage besides reducing the incidence of respiratory distress syndrome.[51,106,107] This reduction of cranial abnormalities has been ascribed to the stabilizing impact of steroids on postnatal blood pressure.[51,108] Likewise, the application of nitric oxide inhalation, used in therapy for respiratory distress syndrome, has been shown to reduce the incidence of severe intraventricular hemorrhage and periventricular leukomalacia.[105,109] Another important change minimizing neurological impairment is depicted by the reduction of the dose of postnatal steroids in chronic lung disease treatment.[51] This reduction has been recommended by the American Academy of Pediatrics in 2002, since postnatal steroids, in particular Dexamethason, have been proven to impair cortical growth.[68,110] All in all, the changes in treatment resulted in a distinct reduction of severe cranial abnormalities from 22% in 1982 to 8% in 2002.[68] It is most likely that this reduction accounts in a large way for the decrease in non-right-handedness over the past couple of years.

In order to answer the question of whether the diminution of any other morbidity in particular further reduced the likelihood of manual transfer, one has to investigate the relation between the different neonatal morbidities and non-right-handedness. Therefore, statistical analysis was performed. Concerning this testing, it has to be considered that the validity of the statistical analysis was reduced due to multiple inclusions. Resulting from the multimorbidity, an interaction between the different morbidities cannot be ruled out and the effect of a single morbidity can only be evaluated in a limited way. Since children with intraventricular hemorrhage grade IV were excluded from the study cohort, the association between this severe cranial abnormality and handedness was not reviewed. Likewise, the suspected relation between meningitis and handedness was not reassessed, as no non-right-handed child in the study cohort suffered from this medical condition. Exploring the association of other neonatal morbidities suspected of having the potential to enhance the likelihood of left-handedness, the current study was not able to verify a statistically significant association between any of the medical conditions and non-right-handedness, except for infection. However, one has to consider the small size of the cohort of non-right-handed children, which only comprised 30 or less ELBW infants depending on the study group, when assessing these results. The small cohort size might have blurred possible associations. The fact that non-right-handedness was less prevalent in subgroups I and II of the Charité ELBW cohort compared to the main group, just as it was less prevalent in the ELBW cohort of the Charité compared to the ELBW reference cohort, strengthens the assumption of a relation between neurological impairment and non-right-handedness, even though the statistical analysis was not able to show any association. Likewise, the failure to confirm the interaction between IVH (grade I, II, III) and handedness, which has been described in earlier studies[57], and the fact that non-right-handed children showed a higher incidence of most medical conditions, even though not statistically significant, underlines the importance of pursuing this approach in order to reveal possible associations in a greater study cohort. Considering the increase of infection in non-right-handed children, one has to take into account that this rise was only detectable in subgroup I and could not be verified in the other two study groups. Hence, this significant distinction between right-handed and non-right-handed children in subgroup I is probably coincidental and the result of multiple testing.

Summing up, even though the cause of the decrease in non-right-handedness is still unknown, one can speculate that the improved general health condition of the early born on the one hand and the reduction of particular neonatal morbidities like IVH, which promote the occurrence of non-right-handedness, on the other hand, have had an effect on the prevalence of non-right-handedness. The abnormalities responsible for the handedness shift may also be minor and eventually not detectable by imaging as suggested by Marlow et al.[30] A greater study cohort is needed to estimate the effect of the different medical conditions on handedness in particular.

4.6 Cognition and Handedness

While the rate of morbidity was reduced in ELBW survivors, the rate of cognitive deficits still remains high. Mikkola et al. only found 26% ELBW children in their cohort who were normally developed at the age of 5 years, implying that 74% of the children showed deficits of some kind.[63] While this increase in cognitive deficits has been well documented and examined in several studies, a possible association between these cognitive deficits in preterm children and their handedness has only been rarely investigated. The few studies focusing on this possible interaction showed contradicting results, with some studies supporting a relation[29,31] and others not finding any relation.[22,67] The ones supporting a relation attribute it to a mild form of unilateral brain-injury, which likewise results in a handedness shift and lowered cognitive abilities.[66]

Trying to shed light on this uncertainty, the present study contrasted the cognitive abilities of non-right-handed and right-handed children. No statistically significant differences in performance in intelligence tests were detected. These results back up the assumption that there is no connection between cognition and handedness. Hence, one has to assume that the factors causing a cognitive deficiency in extremely preterm infants are not linked with the ones causing non-right-handedness. This might result from the injury or disturbance, which causes the lowered cognitive abilities of ELBW children, being too mild to provoke a manual shift.

The median overall IQ scores for all 3 study groups were within the normal limits. When comparing the intellectual abilities of the different years of birth, an increase in IQ values was detected, indicating a rise in cognitive abilities. However, this rise within the different years of births was only observed in subgroup I. Hence, one can suspect that this trend in cognitive abilities resulted from a play of chance, eventually related to the fact that the testing was performed by different psychologists.

4.7 Differences in females and males

The current study results showed an uneven distribution of handedness in female and male ELBW infants. Boys showed a significant higher prevalence of non-right-handedness compared to girls. The data agrees with prior study results on handedness, which showed that females tend to be more dextral than males.[3,6,34,35,111-114] In their meta-analysis from 2008, which included 43 different studies conducted in several countries all over the world, Sommer et al. detected a 25% higher prevalence of non-right-handedness in males.[115] Looking more specifically at ELBW infants, Saigal et al. investigated the prevalence of non-right-handedness in an ELBW group and a control group. In both groups, the male individuals showed a higher prevalence of non-right-handedness. While the prevalence of non-right-handedness among ELBW males was 36% compared to 26% for females, corresponding figures for the controls revealed a prevalence of 23% in boys and 15% in girls.[22]

Therefore, the present study results are consistent with prior findings and suggest that male individuals show a higher prevalence of left-handedness no matter if term or preterm born.

The two major genetic models, the one of McManus and the one of Annett, attribute this increase to a higher probability of the occurrence of chance in male individuals.[90,116] Contrasting these genetic approaches, Geschwind & Galaburda attribute the difference in left-handedness in males and females to the different hormonal constitution. They suggest that high intrauterine levels of testosterone promote the development of left-handedness by delaying the maturation of the left hemisphere. Since male brains are exposed to substantially higher testosterone levels than female one during prenatal development, one would expect an increase in left-handedness in males.[35,117,118]

When looking at the differences in handedness of male and female ELBW infants, it has to be taken into account that preterm birth has been shown to have a greater impact on boys compared to girls, with male ELBW children showing an increased mortality[54,65] and morbidity[55]. It might be suspected that this increase in morbidity further increases the chance of non-right-handedness in preterm boys. However, this theory cannot explain the rise in non-right-handedness of male ELBW children in the present study cohort, since the ELBW boys did not show a significant excess in morbidity.

One has to raise the question why the current study results on male and female morbidity deviate from prior findings. When comparing the number of boys suffering from specific neonatal morbidities to the number of girls, it became evident that boys showed a rise in medical conditions, even if not statistically significant. The failure to attain significantly varying data might result from the cohort being too small in size.

Likewise, the present study results for cognitive abilities differed from prior findings. While no distinct variation in cognitive abilities between male and female ELBW infants was observed in the contemporary ELBW study cohort, older studies of Marlow and Brothwood supported an increase in cognitive deficits in ELBW boys.[53,65] They ascribed this reduction of intellectual abilities among male ELBW infants to a greater biological vulnerability of boys[53], which not only increases the risk of morbidity and mortality (as described above) but also of cognitive deficits in preterm infants. However, the different cohort selection of the two studies has to be considered. While Marlow and Brothwood included children suffering from severe cranial abnormalities[53,65], the present study excluded all children affected by high grade IVH. Taking the effect of the cohort selection into account, a concept of inferior repair capacities in boys appears to be more suited to explain the phenomena than the concept of biological vulnerability. Through the exclusion of all children suffering from severe cranial abnormalities, the inferior repair capacities of male ELBW infants did not come into effect. Therefore, the male and female ELBW children of this study did not show any differences in their cognitive abilities. At the same time, the concept of inferior repair capacities is just as suitable as the concept of biological vulnerability to explain the greater impact of preterm birth on boys.

4.8 Conclusion

In this study the contemporary, local ELBW cohort showed an increase in non-right-handedness compared to the normal population. The corresponding figures of the comparison group confirmed this rise in non-right-handedness in ELBW children.

These findings are consistent with older study results, which suggested an increase in left-handedness in preterm children. However, the rise is not as prominent now as it used to be. The trend towards a lowered incidence of non-right-handedness in ELBW infants became particularly obvious in subgroup II of the ELBW study cohort, in which all children suffering from neurological impairment were excluded. Nevertheless, the comparison group of the Berlin Senate Department of Health and Social Services, which included children with brain injuries and other neurological disorders, also confirmed this trend. The reason for the decrease in non-right-handedness over the past decades still remains unknown.

Speculating, one could either consider the findings of O'Callaghan et al. to be a play of chance or one could ascribe the decrease in non-right-handedness in ELBW infants to the improvements in neonatal treatment. Since the ELBW children without neurological disorders showed the lowest probability of non-right-handedness, the influence of the changes in neonatal medicine on handedness should be further examined in studies with larger ELBW cohorts. A greater number of ELBW children still might possibly reveal a link between the various neonatal morbidities and handedness.

No association between handedness and cognition was detected, indicating that right-handed and non-right-handed preterm children do not differ in their cognitive abilities. Nevertheless, associations between handedness and other dimensions of neurodevelopmental abnormalities such as hyperactivity, attention disorders, emotional problems or dyslexia cannot be ruled out and should be the topic of further investigation.

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„Ich, Christina Rees, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Handedness of former preterm infants < 1000 grams birth weight, association with neonatal complications and cognition at 5 years of age“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
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Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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