UNIVERSITÀ DI PISA

Dipartimento di Medicina Clinica e Sperimentale
Dipartimento di Patologia Chirurgica, Medica, Molecolare e dell'Area Critica
Dipartimento di Ricerca Traslazionale e delle Nuove Tecnologie in Medicina e Chirurgia

Corso di Laurea Magistrale in Medicina e Chirurgia

Neurological Assessment of Infants with Cerebral Arterial Ischaemic Stroke

Tesi di Laurea

Candidata:
GIULIA VAGELLI

Relatore:
Chiar.mo Prof. GIOVANNI CIONI

Tutors:
Prof.ssa CHRISTA EINSPIELER
Dr. ANDREA GUZZETTA

ANNO ACCADEMICO 2014/2015

INTRODUCTION

Arterial Ischaemic Stroke (AIS) occurs in approximately 0.25% of full term infants and around 1% of preterm infants. Up to 60% of perinatal strokes results in neurological deficits, with hemiplegic cerebral palsy (HCP) being a frequent adverse motor outcome. This is a lifelong condition that affects the daily living and the quality of life of these children and their families and often it is diagnosed only after the first year of life or even later, when significant asymmetries in upper extremity function and motor skill development are obvious. This is in contrast to adults who have a stroke who are identified with hemiparesis days not years after the brain injury.

Motor outcomes in neonates with stroke are largely dependent on the location of the injury. The most common presenting feature of neonatal term infants with AIS is seizure and other common presentations include encephalopathy, apnea, tone abnormalities as well as persistent respiratory and feeding difficulties. Physical disability can range from minimal (e.g. weakness in one hand without discernible effects on activities of daily living) to profound (e.g. permanently restricted to a wheelchair and unable to eat or speak independently requiring 24h care).

Today's neuroimaging techniques such as ultrasound, computed tomography and magnetic resonance imaging, provide the possibility to identify brain lesions that may cause hemiplegia. Together with the classical neurological examination, these tools give us the possibility to perform prospective studies of the neurological development of these infants.

What is still missing is a method that could help us for an early diagnosis of future neurological disabilities. There is actually no proof that early intervention could prevent the development of cerebral palsy in these infants, but it could help prevent secondary defects such as contractures and other forms of immobility, improving their future life.

Many studies have confirmed that Prechtl's Method of Qualitative Assessment of General Movements of infants is one of the most powerful predictive tools that we have. The General Movements Assessment (GMA) is a non-intrusive, reliable, quick and cost-effective method of functional assessment of the young nervous system developed by Heinz Prechtl and his colleagues of the Department of Developmental Neurology in Groningen (The Netherlands). This assessment is based on the observation of video-recordings showing the child during his spontaneous motility, with nobody neither touching nor stimulating him. By observation we could be able to distinguish between normal and abnormal general movements.

Normal General Movements are gross movements involving the whole body; they may last from a few second to several minutes or longer. What is particular about them is the variable sequence of arm, leg, neck and trunk movements. They wax and wane in intensity, force and speed and they also have a gradual beginning and end. The majority of sequences of extension and flection movements of arms and legs is complex, with superimposed rotations and frequent slight changes in the direction of the movement. These additional components make the movement fluent and elegant and create the impression of complexity and variability.

Abnormal General Movements are movements lacking complexity, variability and fluency. They could be poor in their quality, or cramped synchronized or even chaotic. These features can be related to some neurological deficits, which can range from cerebral palsy to mild neurological disabilities.

Previous studies highlighted the important predictive power of *Fidgety movements*, which emerge around 6-9 weeks of post-term age. Fidgety movements are small movements of moderate speed and variable acceleration of neck, trunk and limbs, in all directions, continual in the awake infant, except during focused attention, fussing and crying. They may be seen as early as 6 weeks but usually occur around 9 weeks and are present until 20 weeks or even a few weeks longer, at which time intentional, goal directed, and antigravity movements occur and start to dominate. The absence of fidgety movements is highly predictive for later neurological impairments, particularly for cerebral palsy, both the spastic and dyskinetic forms.

General movements can be observed also in fetuses as young as nine weeks postmenstrual age (age of the fetus or infant calculated from the date of the mother's last period), that is why this method can be of a real support for an early diagnosis.

In our study we tried to use this method on a population of 22 full-term infants, 6 were healthy infants, while 16 have been diagnosed with perinatal arterial ischaemic stroke. The aim of this study was to confirm the predictive value of the qualitative assessment of spontaneous motor activity, together with the evaluation of the Motor Repertoire and the assessment of asymmetries in various body parts.

We wanted to analyse to what extent the long-term neurological outcome of infants diagnosed with neonatal stroke is related to their motor performance at age 3 to 5 months; to confirm the predictive power of the quality of fidgety movements and the significant correlation between asymmetry of segmental movements and the presence of later hemiplegia in infants with neonatal stroke; to find a correlation between severe neurological outcome and asymmetry in hand movements, kicking, trunk bending and foot-foot contact and to confirm or reject the theory of the *silent period* that would prevent an early diagnosis of unilateral CP.

ABBREVIATIONS

AIS	Arterial Ischaemic Stroke
PAIS	Perinatal Arterial Ischaemic Stroke
NIH	National Institutes of Health
HCP	Hemiplegic Cerebral Palsy
HIE	Hypoxic-Ischaemic Encephalopathy
MCA	Middle Cerebral Artery
US	Ultrasound
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
DWI	Diffusion Weighted Imaging
CHD	Congenital Heart Diseases
rTMS	repetitive Transcranial Magnetic Stimulation
CIMT	Constraint-Induced Movement Therapy
GMs	General Movements
PMA	Post Menstrual Age
CPG	Central Pattern Generators
CP	Cerebral Palsy
ADHD	Attention-Deficit Hyperactivity Disorder
MND	Mild Neurological Disability
NE	Neurological Examination
HINE	Hammersmith Infant Neurological Examination
MOS	Motor Optimality Score
FMs	Fidgety Movements

Chapter 1

NEONATAL CEREBRAL ISCHAEMIC STROKE

The World Health Organization in 1978 defined stroke as 'a clinical syndrome typified by rapidly developing signs of focal or global disturbance of cerebral functions, lasting more than 24 hours or leading to death, with no apparent causes other than of vascular origin'.

Arterial ischaemic stroke (AIS) is a 'clinical stroke syndrome due to cerebral infarction in an arterial distribution' and perinatal arterial ischemic stroke (PAIS) has been defined by the NIH workshop on Perinatal Stroke as a condition with acute encephalopathy, seizures, or neurologic deficit presenting in the term or preterm infant before the 29th postnatal day, with brain imaging confirming a parenchymal infarct in the appropriate arterial territory[1, 2].

Perinatal ischaemic stroke affects neonates i.e. occurring between 20 weeks gestation and 28 days postnatal life and it is considered a separate entity from 'childhood stroke', which is ischaemic (55%) or haemorrhagic (45%)[3] and includes children in the non-neonatal age-group i.e. 1 month-16 years.

AIS is the commonest cause of hemiplegic cerebral palsy[4](the prevalence reaches 87%[5]) This lifelong condition has implications for performance in activities of daily living, quality of life and self-esteem[6]. Adults with hemiplegic cerebral palsy (HCP) are less likely than their peers to live independently or be in full-time employment.[7]

Perinatal arterial ischaemic stroke is common and produces a significant morbidity and severe long-term neurologic and cognitive deficits, including cerebral palsy, epilepsy, neurodevelopmental disabilities, behavioural disorders, and impaired vision and language functions[1, 8-10]. The maturational stage of the brain at the time of injury is a key factor in the pattern of brain damage, including regional and cell type-specific susceptibility.

1.1 *Classification*

Perinatal AIS can be subclassified according to the time of diagnosis as *fetal*, *neonatal* and *presumed perinatal* AIS:

- *fetal* AIS is diagnosed before birth through the use of fetal imaging methods or in stillbirth on the basis of neuropathologic examination that reveals a pattern of ischaemic brain injury in an arterial distribution;
- *neonatal* AIS constitute an acute presentation of encephalopathy manifesting as seizure, altered mental status, and/or neurological deficit between birth and twenty-ninth postnatal day for which a pattern of ischaemic brain injury in an arterial distribution is evident by clinical neuroimaging. It could be *term* or *preterm* neonatal AIS, according to the gestational age of the infants;
- *presumed perinatal* AIS is diagnosed in individuals >28 days of age with focal neurological deficits and a corresponding chronic infarct in arterial distribution in whom it is presumed (but not proven) that the ischaemic injury occurred between the twentieth week of fetal life through the twenty-eight postnatal day but was not detected during that period[1, 11-13] ('missed symptomatic perinatal strokes'[5]). However, there are often significant delays between onset of parental concern and final diagnosis of presumed perinatal stroke, the latter reported to occur at a mean age of 12.6 months.[11]

1.2 *Epidemiology*

Perinatal AIS occurs in 1 in 2300 to 1 in 5000 live infant births and the estimated mortality rate of neonatal stroke is 3,49/100000 annually[9], it ranges from 2 to 20%, with survivors incurring disabilities that include cognitive impairment in 25 to 70%, motor in 10 to 67%, and epilepsy in15 to 40%.[14, 15]

It has been suggested that the incidence of PAIS is higher in preterm born infants, but this might also reflect the routine use of cranial ultrasound in preterm infants[16].

In term neonates, AIS is the most common recognised cause of Cerebral Palsy and is the second most common underlying etiology of neonatal seizures[17, 18]. These likely are

underestimations, as to some degree neonatal brain imaging may be less commonly acquired in remote or low resource settings[19]. These may be arterial ischaemic strokes, or periventricular venous infarctions, which are due to compression of the medullary veins following germinal matrix haemorrhage prior to 34 weeks gestation[20]. Smaller numbers of cases are due to intracerebral haemorrhage or venous sinus thrombosis.

Up to 60% of perinatal strokes result in neurological deficits[21] with hemiplegic cerebral palsy being a frequent adverse motor outcome. Following a perinatal stroke, approximately 60% of children have CP (usually presenting as a spastic hemiplegia), 30-60% experience epilepsy, 25% show language delay, and up to 22% manifest behavioural abnormalities (defined as physician diagnosed attention, hyperactivity or behavioural problems)[22].

To complicate things further, although most cases presenting as presumed perinatal stroke will become confirmed cases of hemiplegic cerebral palsy[22], this is not true for symptomatic perinatal stroke. Of the patients presenting in the neonatal period with symptomatic stroke, around 50% develop cerebral palsy and around 35% may have normal outcome, with the rest having relatively minor motor abnormalities.[5] Clearly, this is important when considering whom to target with early intervention.

A male predominance of approximately 60% occurs in term neonatal AIS but has not been observed in preterm neonatal AIS[11-13, 23]. Many central nervous system diseases display sexual dimorphism. Stroke, cerebral palsy, and related developmental disorders are more common in males than in females, but the reasons of these differences remain uncertain. Sex hormones can provide protection against ischaemic injury, but the neonatal brain may not be as influenced by these hormones as the adult brain.

1.3 *Risk factors*

The maternal-fetal dyad, present in pregnancy and at delivery, gives rise to specific etiologic considerations with regard to neonatal stroke. Risk factors for perinatal AIS comprise maternal, neonatal and placental conditions (**Table 1**). Maternal risk factors include infertility, preeclampsia, prolonged rupture of membranes, maternal smoking, intrauterine growth retardation, maternal fever, thrombophilia and chorioamnionitis.

Pathologic changes resulting in gestational diabetes, pregnancy-induced hypertension and preeclampsia have long been linked to neonatal stroke[24]. Preeclampsia reduces placental

blood flow, resulting in fetal cerebral hypoperfusion and the potential for emboli or global or focal ischaemic injury. In case control studies, factors present at delivery including fetal bradycardia, fetal decelerations, prolonged rupture of membranes or prolonged second stage of labor are associated with neonatal stroke, although it remains unclear whether these represent a casual relationship, or are reflective of intrauterine or ongoing stroke. Additional risk factors associated with difficult delivery such as vacuum delivery and emergency of Caesarean section are associated with an increased risk of neonatal stroke. A recent study identified an Apgar score of <7 at 5 minutes, as well as maternal fever >38°C and hypoglycaemia as independent risk factors for perinatal stroke[25, 26]. Mechanical force applied to newborn's head and neck during labor may also lead to injury of craniocervical arteries increasing risk of arterial dissection and stroke[27].

Increasing evidence suggest that the placenta has a significant role in neonatal neurologic disorders. Placental abruption with resultant decreased perfusion has been associated with neonatal stroke as well as hypoxic-ischaemic encephalopathy (HIE). Additionally, placental chorioamnionitis even in the absence of maternal symptomatology is associated with neonatal stroke. Previous studies in which infants and children were diagnosed with cerebral palsy, later in life and in whom the placenta was available for pathologic examination, often showed a high incidence of chronic infarctions, vascular pathology, anomalies of umbilical cords insertion or length of the umbilical cord or vessels[28, 29].

Risk Factors for Perinatal Arterial Ischemic Stroke

Type of Risk Factor	Risk Factor
Maternal	Thrombophilia
	Infertility
	Prolonged rupture of membranes
	Preeclampsia
	Smoking
	Intrauterine growth retardation
	Infection
	Maternal fever
Fetal	Thrombophilia
	Congenital heart disease
	Arteriopathy
	Hypoglycemia
	Perinatal asphyxia
	Infection
	Need of resuscitation
	Apgar score of <7 at 5 minutes
Placental	Chorioamnionitis
	Placental infarcts
	Placenta weighing less than tenth percentile

Table 1[30]

Pregnancy is considered to be a natural pro-thrombotic state[1] because it is associated with changes in haemostasis due to evolutionary changes to protect the pregnant mother from fatal haemorrhage at the time of delivery. These changes predispose the mother to thromboembolism and place the fetus and the placenta at risk for thromboemboli. During pregnancy, coagulation factors V, VII, VIII, IX, X, XII, von Willebrand factor and plasma fibrinogen concentrations significantly increase[31]. Concomitantly, fibrinolytic activity is decreased in pregnancy, and returns to normal within 1 hour after placental delivery.

The presence of at least one pro-thrombotic factor substantially increased the incidence of stroke from 24% in neonates in the control group to 68% of 91 term neonates[32]. Increased lipoprotein (A) is considered one of the most important pro-thrombotic risk factor in newborns. Other common pro-thrombotic factors associated with neonatal stroke include genetic polymorphisms of MTHFR (C677T), Factor V Leiden (G1691A), and prothrombin (G20210A)[32-36]. Acquired pro-thrombotic states of anticardiolipin antibodies, activated protein C or protein S deficiency, or antithrombin deficiency also have been linked to neonatal stroke[33-36]. These factors in combination with other trigging factors such as neonatal septicaemia, perinatal asphyxia or patent foramen ovale may potentiate the risk of stroke.

Infants with congenital heart disease are at higher risk for perinatal stroke although the incidence is not clearly known[37]. Neonates with CHD have been found to sustain arterial stroke in patterns of arterial occlusive or watershed injury. AIS has been found to occur in the preoperative and intraoperative and/or postoperative periods[38]. Many operative features and diagnostic procedures have been associated with the occurrence of AIS in neonates.

Fewer studies exist that examine maternal risk factors in preterm infants with *neonatal* AIS. Golomb et al. [39] examined infants with preterm neonatal AIS and found that 30% of the mothers had a history of maternal infection, 22% had a history of gestational bleeding, 17% had a history of maternal smoking, and 9% had a history of maternal drug use. Benders et al.[16], on the other hand, was not able to demonstrate any relationship between preterm neonatal AIS and any known maternal risk factor.

Even fewer studies have examined maternal risk factors in *presumed perinatal* AIS.
Golomb et al.[39] found that most of the children diagnosed with presumed perinatal AIS had maternal histories of preeclampsia, maternal infection, bleeding during pregnancy, or gestational diabetes.

1.4 *Clinical presentation*

Newborns who sustain AIS present 58-68% of the time during the neonatal period.[22, 34] The remainder presents after 28 days of age usually because of detection of a focal neurological abnormality, which, in turn, leads to discovery of an old cerebral infarct that is classified as presumed perinatal AIS. The most common presenting feature of neonatal term infants with AIS is seizure. Seizures constitute the initial sign in 69-90% of the term newborns with AIS.[22, 34, 40] The first seizure occurrence after 12 hours of life, especially one with focal features, has been reported to distinguish those days AIS rather than generalized hypoxic-ischaemic brain injury.[41] Further, most of the seizures associated with neonatal AIS occur within the first 3 days of life.[22, 26, 42] Other common presentations include encephalopathy, apnea, tone abnormalities and persistent respiratory and feeding difficulties.

Epilepsy and motor impairment occurs in approximately one-half to two-thirds of injured neonates.[1, 24, 25, 39, 43-45] Reports on the occurrence of recurrent seizures after perinatal arterial ischaemic stroke has ranged between one-quarter and two-thirds of stroke size associated with likelihood of seizures beyond the acute period[46]. Seizures may also be subtle and may remain unnoticed, causing a delay in diagnosis.

Some infants may show asymmetry of tone during the first days to weeks, with hypotonia rather than hypertonia on the affected side. Infants may, however, remain asymptomatic.[47]

Motor outcomes in neonates with stroke are largely dependent on the location of injury. The internal capsule as well as the deep grey matter involving the basal ganglia more often is associated with neuromotor disability.[21, 48]Cortical involvement in the MCA distribution with involvement of the basal ganglia and the internal capsule is associated with hemiplegia, while those with basal ganglia and internal capsule without cortical involvement also may have motor coordination difficulties[49].

Preterm neonates with AIS present differently from term infants. Preterm infants with neonatal AIS are commonly asymptomatic and are diagnosed by routine head ultrasound.[16, 22] Seizure occurrence is less common as compared to term infants with neonatal AIS. Golomb et al.[50]found that the most of the preterm infants with neonatal AIS presented with respiratory difficulties or apnea (83%), whereas 30% presented with seizure, 26% with abnormal feeding, and 22% with abnormal tone.

Presumed perinatal AIS usually presents after 2 months of age with a median age of presentation of 6 months.[22, 39] Most infants (81-81%) with presumed perinatal AIS present with early hand preference or fisting[5, 44].

1.5 *Evaluation*

Patient evaluation after perinatal AIS focuses on identification of etiologies that may increase the risk of a recurrent event. Occurring at an approximate rate of 2%, recurrent events have been associated with pro-thrombotic disorders, CHD (congenital heart diseases), and arteriopathy.[51, 52] Therefore, evaluation should include laboratory testing for thrombophilia, an echocardiogram to evaluate for intracardiac thrombus, right-to-left shunt or structural features contributing to cardioembolic stroke, and vascular imaging of both head and neck to evaluate for craniocervical arteriopathy.

1.6 *Diagnosis: EEG and Imaging*

An amplitude-integrated EEG (**aEEG**) or full EEG should be obtained in any infant presenting with neonatal seizures and may help to localise the origin of the seizures. In the case of Perinatal AIS, aEEG may further assist in predicting development of motor outcome, which is often worse following the persistence of abnormal background activity on the affected side[43].

From neonatal age onwards, neuroimaging techniques such as US, CT, or MRI, provide the possibility to identify brain lesions (cerebral infarctions, brain malformations, etc.) which may cause hemiplegia. Consequently, it is now possible to perform prospective studies of the neurological development of these infants. Bouza et al.[53] reported that term infants with middle cerebral artery infarction and later hemiplegia either had a normal neurological examination or subtle transient abnormalities until they were 6 months of age.

In preterm infants a unilateral periventricular lesion, very likely as a result of a venous infarction, is the type of brain damage most frequently associated with congenital hemiplegia[54, 55]. This lesion can be easily identified by cranial US[56].

Clinical suspicion of neonatal AIS is confirmed by neuroimaging.

Cranial ultrasound is the most convenient but also the least sensitive of available neuroimaging modalities.[57, 58] It is often the first imaging modality used in infants who are suspected of cerebral injury; if it is performed shortly after the onset symptoms, scans may still appear normal. In a study of serial cranial ultrasound exams of 47 infants with PAIS, sensitivity increased from 68% in the first three days to 87% between day 4 and 10.[57] Cranial ultrasound is operator dependent and detection of PAIS may therefore differ between centres.

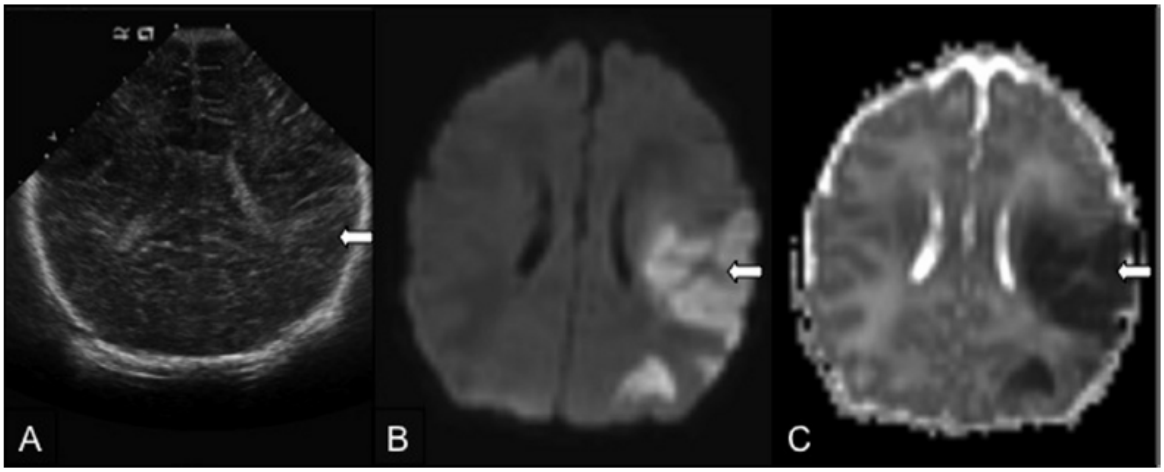
Cranial computer tomography offers higher image resolution than ultrasound but exposes the infant to x-irradiation.

Magnetic resonance imaging (MRI) provides the highest anatomic resolution and the best sensitivity to detect acute ischemia but requires transport of the patient to an MRI scanning suite (**Figs 1.1 and 1.2**)[59]. It is one of the two most effective early predictors of motor outcome following symptomatic perinatal stroke together with the assessment of general movements (see Chapter 2).

Specific sequences important to obtain when imaging the neonate with MRI include diffusion-weighted imaging (DWI), T_1- and T_2-weighted imaging (T_1W and T_2W), and susceptibility weighted imaging. A magnetic resonance angiography (MRA) of the head and neck should be considered to look for craniocervical arteriopathy because it can easily be added to the initial MRI evaluation. Vascular imaging has not been studied as much in neonatal stroke as it has in older children and adults. Nonetheless, patient reports and series have demonstrated the ability of MRA to detect cervicocephalic arterial dissection and asymmetry of cerebrovascular trees in neonates found to have AIS.[27, 60-62] Phase contrast MRA can be used to quantify the blood flow in large vessels and may indicate asymmetry in carotid blood flow due to hypoperfusion or hyperperfusion[63].

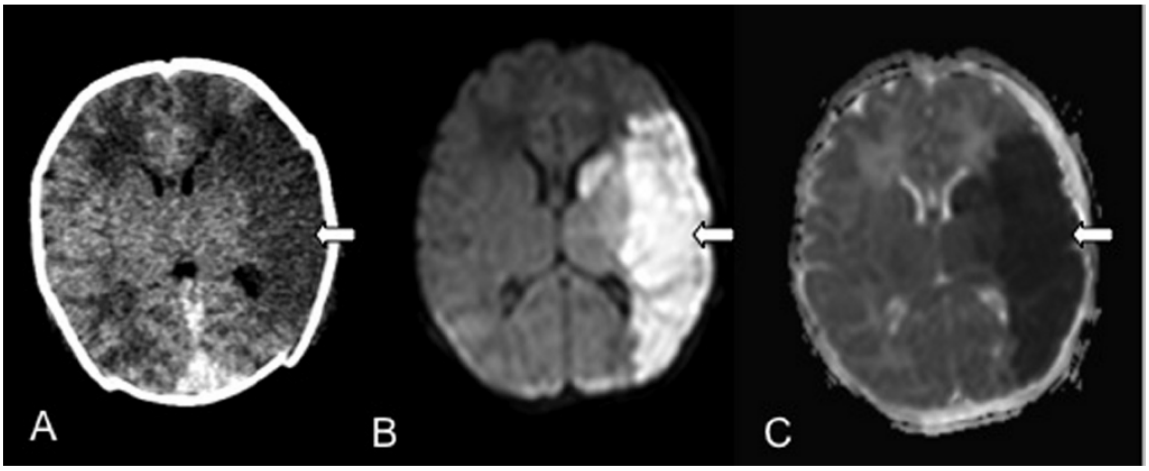
Different MRI sequences are helpful to identify perinatal stroke depending on the timing of the imaging from the initial injury. DWI is used to see cytotoxic oedema[a] and in neonates is sensitive within hours of the initial injury, similar to adults. Visualization of the lesion using DWI is best observed within the first 2-4 days from the time of the initial injury.[64, 65]

[a] Experimental studies have shown that the rapid shift of water from the extracellular space to the intracellular space, resulting in cytotoxic oedema, can be assessed within minutes as increased signal intensity on DWI. Changes on DWI can, therefore, precede those on conventional T1WI and T2WI and are often seen more clearly on DWI during the first 24-72h. The changes are characterised by high signal intensity on DWI or low signal intensity on the derived apparent diffusion coefficient (ADC) map. The lowest ADC can be observed around day 3, after which ADC values will slowly increase[58]. At approximately 6-10 days after the injury, ADC values in the ischaemic tissue appear to have normalised, so-called *pseudonormalisation*, at which point DWI is of limited value in diagnosing PAIS.



Comparison of head ultrasound (HUS) and brain magnetic resonance imaging (MRI) of neonatal arterial ischemic stroke in a 1-day-old term infant who presented with a right focal seizure. (A) HUS reveals hyperechogenicity in the left cerebral hemisphere (indicated by white arrow) concerning for ischemic injury. (B) Axial MRI diffusion-weighted trace image of the same patient observed in (A) reveals well-defined hyperintensity (indicated by white arrow) in the left middle cerebral artery (MCA) territory. (C) Diffusion-weighted image apparent diffusion coefficient map of matching slice observed in (B) reveals corresponding hypointensity (indicated by white arrow) in the left MCA territory.

Fig. 1.1

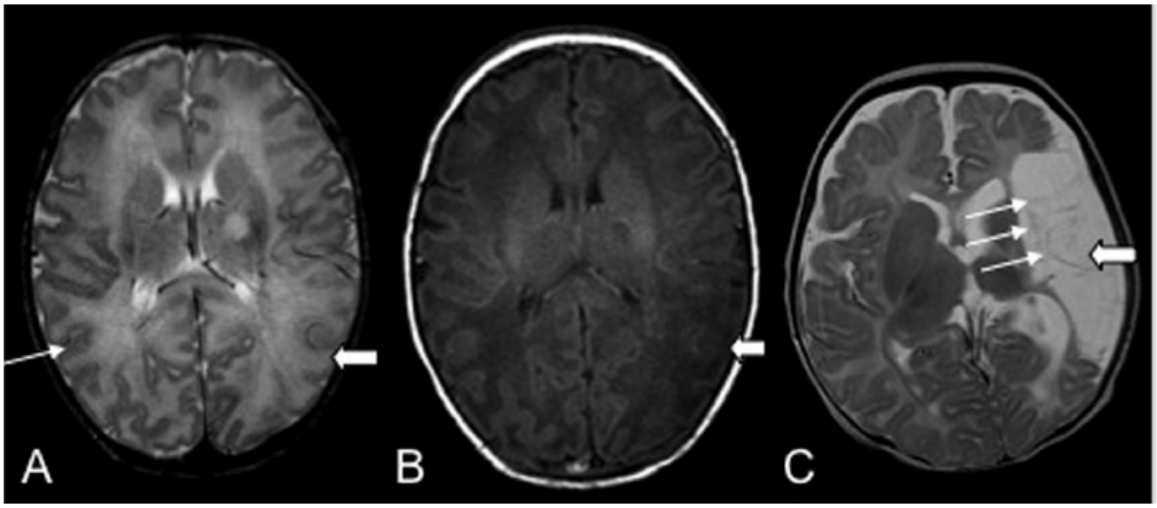


Comparison of cranial computed tomography (CCT) and brain magnetic resonance imaging (MRI) for demonstration of neonatal arterial ischemic stroke in a 1-day-old term infant who presented with a right focal seizure. (A) An axial CCT image reveals hypodensity (white arrow) in the left middle cerebral artery (MCA) territory consistent with acute infarction. (B) Axial MRI diffusion-weighted trace image of the same patient revealed in (A) reveals clearly demarcated area of infarct as a region of hyperintensity (white arrow) in the left MCA territory. (C) Diffusion-weighted image apparent diffusion coefficient map reveals region of signal hypointensity and restricted diffusion (white arrow) to match area of signal hyperintensity observed in (B).

Fig. 1.2

Dudink et al. studied term infants with neonatal stroke in the first postnatal weeks with MRI to find that T_2W images revealed a high signal intensity in affected cortical grey matter and white matter during the first week of life, whereas T_1W imaging revealed a low signal intensity in the involved cortical grey matter. From 1 week to 1 month after birth, cortical grey

matter signal intensity was high on T_1W imaging (the so-called "cortical highlighting") and low in T_2W imaging. After 1-2 months the infarcted area evolved into area of tissue loss and cysts (**Fig. 1.3**)[65].



Comparison of magnetic resonance imaging (MRI) appearance of a patient with acute neonatal arterial ischemic stroke (AIS) compared with MRI of a patient with presumed perinatal AIS. (A) T_2-weighted (T_2-W) axial image obtained in a 1-day-old term infant who presented with seizure reveals hyperintensity (thick arrow) in gray matter cortex and underlying white matter with loss of gray and/or white matter differentiation in the left middle cerebral artery territory (thick arrow) consistent with acute infarction compared with the normal right side with dark cortex (thin arrow) and normal differentiation of the white and gray matter. (B) T_1-weighted axial image, obtained in the same patient at the same time as image in (A), reveals signal hypointensity in cortical gray matter (white arrow) matching the area of hyperintensity observed in (A) consistent with a diagnosis of acute neonatal AIS. (C) T_2-W image obtained in a 3-month-old infant with an unremarkable neonatal history who presented at 3 months of age with a prematurely appearing right-hand preference reveals an area of hyperintensity and cystic change (thick arrow) with cystic septations (thin arrows) typically of chronic infarction.

Fig. 1.3

In all types of perinatal AISs, the majority are unilateral, occur in the left hemisphere and in the middle cerebral artery (MCA) territory. In a recent study of preterm and term neonatal AIS and presumed perinatal AIS, Lee et al. found that 87% of strokes were unilateral. The majority occurred on the left side (53%) compared with those on the right (35%) alone. MCA territory was exclusively affected in 74% of patients.[22] Other studies have confirmed the predominance of left hemispheric (58-64%) and MCA territory locations (75-90%) of AIS found in preterm, term neonates, and those identified as presumed perinatal AISs.[16, 26, 39]

The location of AIS within the MCA territory varies in term and preterm neonates. Term neonates usually demonstrate cortical branch strokes (59%) within the MCA territory while lenticulostriate branch infarcts are commonly observed in preterms (39%).[16, 26] Main branch MCA strokes occur with approximately equal frequency in term and preterm infants. Interestingly, the arterial involvement in the preterm infant was evident to change with

gestational age. Most of the infants with preterm AIS, <28-32 weeks of gestational age, had lenticulostriate involvement compared with older (32-36 weeks of gestational age) preterm infants with AIS, in whom the majority had cortical branch infarcts.[16] These results correlate with findings that most of the term neonatal MCA territory AIS reflects cortical branch involvement.[26]

1.7 *Why aim to intervene early after perinatal stroke?*

Major developmental changes are occurring in the nervous system in the first year of life, with long-term implications for function. One of the most striking of these, highly relevant to motor outcome after stroke, is the ongoing activity-dependent plasticity within descending motor pathways.[66] The corticospinal tract is the major descending pathway from the brain to the spinal cord controlling voluntary movement. At term, corticospinal fibres from each hemisphere project to each side of the spinal cord (bilateral system). Neurophysiological evidence indicates that in healthy infants, gradual progression to a predominantly crossed projection occurs, within the firs 3 years of life, with the most marked changes concentrated within the first year.[67]

Following unilateral perinatal stroke, corticospinal projections from the affected hemisphere are at a competitive disadvantage and, in patient with poor motor outcome, are gradually down-regulated whilst uncrossed projections from the undamaged hemisphere are pathologically retained.[67, 68] Patients with the most favourable functional outcome retain crossed projections from the affected hemisphere[69]. This is true for a variety of lesions type. Though lesions acquired early in pregnancy (such as malformations of cortical development), typically lead to less severe motor dysfunction than those acquired later (e.g. middle cerebral artery territory infarctions) where both have led to pathologically retained uncrossed projections from the undamaged hemisphere. This may reflect a greater capacity for intrahemispheric reorganizational potential earlier in fetal development.[70] Thus, interventions within this early time window after perinatal stroke might have the potential to steer the course of corticospinal tract development towards a more normal pattern, providing a unique opportunity to influence outcome.

Predictions that the course of corticospinal tract development can be altered during this critical time window have been confirmed in animal models by seminal studies by Martin et al.[71]. Electrical stimulation of a unilaterally inactivated corticospinal tract re-established normal connectivity and partially restored motor function in a neonatal cat model[72].

Constraint of the unaffected side, plus encouragement of use of the affected limb, improved motor outcome and restored corticospinal tract connections, spinal cord circuitry and the motor cortical map[73]. Outcome was best when training began early, and training plus constraint was more effective than constraint alone. However, preventing normal limb use very early in development could adversely affect function of that limb long-term.[74]

Immediate and total immobilisation of the unimpaired forelimb, producing forced overuse of the impaired limb (whilst obviously an extreme example), also worsened the neuronal injury in adult rodent stroke models[75]. Thus the nature and risk-benefit ratios of potential intervention strategies must be very carefully explored.

Notwithstanding these dramatic developmental changes during infancy, when the greatest potential effects of the intervention on outcome may be expected, there is also the option for later intervention which exploits ongoing neuronal plasticity. Neurophysiological approaches modulating cortical excitability, and therapy approaches such as constraint, have been shown to influence motor outcome after stroke even in elderly adults. However, in hemiplegic cerebral palsy, morbidity can increase over time -examples being developmental disregard of the affected side and contractures. The earlier the onset of an effective intervention, the more secondary morbidity could hopefully be prevented.[76]

1.7.1 *Pathophysiology and Reorganization after pre- and perinatal brain lesions*

Little is understood about the pathophysiology of perinatal stroke, which means that few disease-specific treatments and no prevention strategies are available.

Studies in mature brain of model organisms have shown that a focal lack of blood flow causes a drop in oxygen and glucose concentration that result in energy failure and changes in ionic concentration. What follows is a complex cascade of intracellular changes that include increased pH, increased glutamate, and increased intracellular calcium.[77] The result is cell death, apoptosis or cell edema. Afterward changes can be seen distal to the injury with altered

metabolism in the injured hemisphere and changes in inhibition or excitation in areas that receive input from the sight of damage[78]. This can lead to secondary cell death or loss of function. In developing brains these processes intersect with the multiple processes of brain maturation such as neuronal maturation, myelination, synaptogenesis, and normal neuronal pruning. Therefore the consequence of ischemia and the resulting degeneration, or potential regeneration, can vary depending on the precise stage of development[78, 79].

There is a longstanding and persistent theory that early injury has less of an effect on long-term outcome than injury later in life because of the capacity of the developing brain to "heal" or compensate[80], that is why the developing human brain can compensate for pre- and perinatally acquired focal lesions more effectively than the adult brain. The mechanism by which this effective reorganization is achieved varys considerably between different functional systems, reflecting differences in the normal maturation of these systems.

In the *motor system*, descending cortico-spinal motor projections have already reached their spinal target zones at the beginning of the third trimester of pregnancy, with initially bilateral projections from each hemisphere. During normal development, the ipsilateral projections are gradually withdrawn, whereas the contralateral projections persist. When, during this period, a unilateral brain lesion disrupts the cortico-spinal projections of one hemisphere, the ipsilateral projections from the contralesional hemisphere will persist. This allows the contralesional hemisphere to takeover motor control over the paretic extremity (**Fig. 1.4**). Although this mechanism of reorganization is available throughout the pre- and perinatal period, the efficacy of this ipsilateral takeover of motor functions decreases with increasing age at the time of the insult.

In the *somatosensory system*, ascending thalamo-cortical somatosensory projections have not yet reached their cortical target zones at the beginning of the third trimester of pregnancy. Therefore, these projections can still 'react' to brain lesions acquired during this period, and can form 'axonal bypasses' around periventricular white matter lesions to reach their original cortical target areas in the postcentral gyrus. In contrast, when the postcentral gyrus itself is affected, no signs for reorganization have been observed. Accordingly, somatosensory functions are often poor in these patients.

Language functions can be normal even in patients with extensive early left-hemispheric brain lesions. This is achieved by language organization in the right hemisphere, which takes place in brain regions homotopic to the classical left-hemispheric language areas in normal subjects. In

patients with periventricular lesions, the degree of right-hemispheric takeover of language functions correlates with the severity of structural damage to facial (and, thus, articulatory) motor projections.[81]

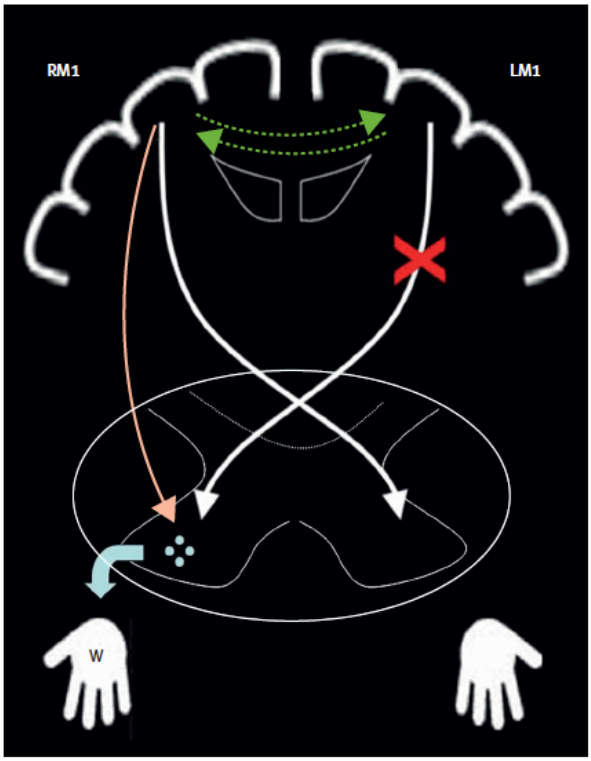


***Figure 7*: Developmental plastic motor organisation after perinatal stroke**
Control of the weak right hand (W) often relies on both contralateral corticospinal pathways from the left (lesioned) primary motor cortex (LM1, solid white line) and ipsilateral projections from the unlesioned right primary motor cortex (RM1, solid orange line). These two inputs compete to establish synapses with anterior horn spinal motor neuron pools (circles) during child development. Additionally, each primary motor cortex can affect the other via interhemispheric inhibition (dashed green arrows). The relative balance of control determines motor outcome, with contralateral control associated with better function. Interventions that promote the success of contralateral (or inhibit the success of ipsilateral) upper motor neuron systems to compete for spinal motor neurons should result in better motor function. Modified from Kirton,[69] by permission of Elsevier.

Fig. 1.4

1.8 *Acute Management*

In contrast to the significant progress that has been made with prevention, diagnosis and management in stroke in adults, management of perinatal stroke remains problematic at each step. In the absence of any obvious primary preventive strategies, the next best option is

"damage control". Neuroprotective strategies (see 1.8.1 *Experimental approaches*) could help minimise tissue damage from the initial insult. However, there are also opportunities for intervention outside this immediate post-injury period.

During the acute phase, therapeutic options are limited and mainly involve supportive measures such as maintenance of normal hydration, electrolytes, glucose, haemoglobin, oxygen and pH levels.[47]

Because recurrence rates are low, treatment of perinatal AIS in the acute setting has been largely supportive. Data are lacking to support prophylactic treatment with an **antithrombotic** after stroke in neonates. The American Heart Association guidelines state that **anticoagulation** may be helpful in patients with perinatal AIS who have either a pro-thrombotic state or CHD.[82] Similarly the CHEST guidelines recommend use of anticoagulation after stroke only for the neonate who has a documented cardioembolic source or who is homozygous for protein C deficiency.[83]

Because a majority of neonates with stroke presents with seizures, **antiepileptic** medication should be considered. Continuous EEG or aEEG is required to recognise subclinical seizures and the effect of antiepileptic medication. Studies on the impact of seizures on outcome in neonatal stroke do not exist. In addition, animal models have demonstrated that post-stroke seizures significantly increase ischaemic lesion volume.[84] These results may be applicable to neonates with AIS who present with seizures and who have recurrent clinical or subclinical seizures, thereafter Kirton et al.[40] found that most of the neonates with neonatal AIS were treated with antiepileptics (67%) initially. However, only 2% were discharged from the hospital on antiepileptic medication, suggesting that treatment duration with antiepileptic medication is usually short. Guidelines on anticonvulsive therapy vary between centres, but often involve phenobarbital as a first-line treatment.

1.8.1 *Experimental approaches*

No standard early approach exists for perinatal stroke. There is a very broad range of experimental approaches whose relative merits remain to be established.

1. MINIMISING DAMAGE FROM THE INITIAL INSULT: NEUROPROTECTIVE STRATEGIES

Therapeutic hypothermia reduces the risk of major neurodevelopmental disability and mortality by around 25% in term and late preterm neonates with hypoxic ischaemic encephalopathy[85]. Side-effects include sinus bradycardia and thrombocytopenia. The mechanism appears to be multifactorial but is broadly relate to reduction in excitotoxicity and inflammation[86]. Hypothermia has not been systematically investigated as an approach to perinatal stroke, but in one study of neonatal encephalopathy, none of 5 patients with focal stroke receiving cooling developed neonatal seizures, in contrast to 7 of 10 similar patients who did not receive cooling[87]. It has been suggested that induced hypothermia is investigated as a therapeutic option in infants with arterial ischaemic perinatal stroke[88]. The evidence from animal models suggests that treatment should begin within 6 hours of stroke in order to be effective[86]. This poses a problem for patients with stroke who do not present with very early onset encephalopathy or seizures.

Other **neuroprotective factors** are also been explored in the context of neonatal brain injury- this has been recently reviewed by Gonzalez and Ferriero[89]. Some of these are surprisingly familiar from other clinical contexts. Such as growth factors (for example erythropoietin[90]that in neonatal rat models decreases cerebral volume loss, increases both neurogenesis and oligodendrogenesis from precursors cells, and improves outcome after stroke), antioxidants (including melatonin), anti-inflammatory agents (including minocycline) and a range of agents aimed at reducing excitotoxic damage (including topiramate).

2. CELL REPLEACEMENT THERAPY: STEM CELL TRANSPLANTATION

Stem cells are cells with the potential for both self-renewal and differentiation into a wide range of cell types. There is much interest in their potential to reduce the burden of morbidity following ischaemic insults to the developing brain[91] . Investigations are being pursued with a range of stem cell types, which are likely to act in different ways. For example, neural precursor stem cells have been shown to migrate to the lesion site following unilateral hypoxic ischaemic injury in neonatal rats; some of the cells then differentiated into glial subtypes, with a small minority differentiating into neural subtypes[92]. In contrast, mesenchymal stem cell transplants from human umbilical cord blood, whilst also migrating to the lesion site, showed little evidence of differentiation into either neural or glial subtypes in a neonatal rat ischaemic stroke model[93]. The reduced infarct volume and improved functional outcome in the transplanted group were attributed to anti-inflammatory effects through release of trophic factors.

The potential risks from stem cell transplantation are high, including tumour development and transplant rejection, and there remain many unanswered questions regarding mode of delivery, mode of action, optimal use, timing etc. However, **autologous umbilical cord blood-derived cells**, which pose a number of obvious advantages from ethical and safety viewpoints, have reached the stage of phase one clinical trials following perinatal arterial ischaemic stroke (ClinicalTrials.gov reference NCT01700166) and acutely in neonatal hypoxic ischaemic encephalopathy (ClinicalTrials.gov reference NCT01506258).[66]

3. MODULATING CORTICAL EXCITABILITY: NEUROPHYSIOLOGICAL APPROACHES

There has been much recent interest in the possibility of modulating cortical excitability using non-invasive brain stimulation to improve outcome after stroke[94]. Cortical excitability is altered following stroke, in infants as well in adults[95], although the precise pattern of alteration differs by lesion location[96]. One of the observed effects in adults following stroke is a high level of interhemispheric inhibitory drive from the intact hemisphere to the affected hemisphere, correlating with poor motor performance of the paretic hand[97]. This finding has driven studies aiming to increase excitability of the affected motor cortex and/or decrease excitability of the unaffected motor cortex. This has been done non-invasively using **transcranial direct current stimulation**[98] (with the anode being excitatory and the cathode being inhibitory), or using **repetitive transcranial magnetic stimulation** (rTMS, with low stimulation rates being inhibitory and high stimulation rates being excitatory)[99].

Low rate rTMS to the unaffected hemisphere has also been studied in older children with subcortical stroke, demonstrating safety and feasibility of the approach[100]. There is an ongoing trial comparing the effect of rTMS and constraint-induced movement therapy in combination with each treatment separately (or neither) on motor outcomes in school-age children with hemiplegia due to perinatal ischaemic stroke (ClinicalTrials.gov identifier NCT01189058). It is a present unclear as to whether such non-invasive brain stimulation approaches are applicable earlier in life after perinatal stroke, when interhemispheric inhibition is still immature[101].

4. THERAPY-BASED APPROACHES WITH ONSET IN INFANCY

The current emphasis on therapy-based interventions remains on children with established hemiplegic cerebral palsy, not on young infants. One approach is **constraint-induced movement therapy** (**CIMT**), in which use of the ipsilesional hand is prevented for a period

of time for example using a restrictive glove. During this time, intensive movement practice is achieved with the contralesional (more-affected) arm and hand. An alternative approach is intensive bimanual therapy. Whilst there remain a number of unanswered questions including the optimal duration and mode of delivery and the effect of the nature and severity of the underlying lesion, there is evidence for the effectiveness of both CIMT and bimanual therapy in this older age group[102].

In the first few years of life, the principle of activity-dependent competition shaping corticospinal tract development might suggest that constraint of the ipsilesional hand would be the more appropriate approach. However, along with increased potential for benefit in this age group comes increased risk from aberrant plasticity. For example, constraint of the ipsilesional hand in infants at risk of hemiplegia may have adverse effects on development of movement control of that hand. The correct balance between promoting use of the contralesional arm and hand versus hindering development of the ipsilesional arm and hand must be struck if constraint is to be used.[103]

Exploitation of the **'mirror neuron system'** is also under investigation as a method of improving motor outcome in children with hemiplegic cerebral palsy. Mirror neurons were first identified in animal studies and were so named because they fired when the animal either performed a motor task or observed the same task being performed.[104] Indirect evidence for a human mirror neuron system has subsequently been presented.[105] Cortical responses to action observation resembling those to action performance have been demonstrated in infants and young children as well as adults[106-108]. There is an increasingly strong evidence that the mirror neuron system is an important component of motor learning. Therapy based on action observation and imitation was shown to improve motor recovery following stroke in adults.[109] A recently published randomised controlled trial indicated short-term improvements in use of the affected hand in bimanual tasks with therapy involving repeated action observation and execution compared with repeated practice alone in 24 children age 5-15 years with hemiplegia.[110] Researchers from the same group have taken on the significant challenge of applying similar approaches to infants with predominantly unilateral brain lesions from the age of 9 weeks.[111]

Of course children with CP will need not only a physical therapy but also speech and language therapy, treatments for problems with eating and drooling, drug treatments to reduce spasticity (diazepam, baclofen, dantrolene sodium and botulin toxin) an eventually

orthopaedic surgery together with orthotic devices, if spasticity and stiffness are severe enough to make walking and moving about difficult or painful.

Chapter 2

GENERAL MOVEMENTS ASSESSMENT AS AN EARLY MARKER FOR CEREBRAL PALSY

Prechtl's method on the Qualitative Assessment of General Movements in Preterm, Term and Young Infants

The nervous system is the most complex and complicated organ of any organism. Neurological examinations of newborns and young infants is mostly based on the study of neonatal reflexes, such as grasping, Moro reflex, rooting, and tonic asymmetric response and evoked responses, such as those involved in passive and active muscle tone. Little attention is paid on the spontaneous activity of the baby.

More than 20 years ago, Prechtl et al [112-114]introduced a new approach to neurological evaluation based on spontaneous motor activity, rather than reflexes and evoked responses. Theoretical and empirical considerations suggest that the quality of endogenously generated motor activity is a better indicator of neural function integrity than many items in the neurological examination. Prechtl et al[113, 115-117] studied movement patterns of fetuses, preterm and term infants and found them to be endogenously generated by the unstimulated nervous system. The rich repertoire of movement patterns that developed in utero continued to be expressed after birth[118]. In fact fetuses and newborn infants exhibit a large number of endogenously generated motor patterns, which are produced by *central pattern generators (CPG)* located in different parts of the brain. We can say that in this period newborns don't want to move, their nervous system is moving them.

Moreover, substantial indications suggest that spontaneous activity is a more sensitive indicator of brain dysfunction that reactivity to sensory stimuli in reflex testing. Well-known examples of CPGs are the central mechanisms for breathing, sucking and chewing, and for locomotion such as swimming, crawling and walking. More recently a better understanding of the cellular and molecular mechanism responsible for endogenously generated motor activity

has been reached (most CPGs consist, in part, of bistable neurons which generate self-sustaining oscillations of membrane potentials and act as pacemaker-like structures) [(119)].

2.1 *What are General Movements?*

The term 'general movements' for this specific pattern was coined by Prechtl et al (1979) in an observational study on spontaneous motility in carefully selected low-risk preterm infants. The subsequent fetal studies on the emergence of the different prenatal movement patterns revealed an onset of GMs at 9 weeks postmenstrual age[(120)]. They continue to be present during the whole prenatal period[(117, 121, 122)]until about 5 or 6 months post-term age.

Normal GMs involve the whole body in a variable sequence of arm, leg, neck and trunk movements. They wax and wane in intensity, force and speed, and they have a gradual beginning and end. Rotations along the axis of the limbs and slight changes in the direction of movements make them fluent and elegant and create the impression of complexity and variability[(112)]. Complexity, Variability and Fluency are the three keywords to describe normal GMs. The assessment of spontaneous GMs in based on visual gestalt perception[b].

GMs have a very long prenatal history. The very first "embryonic movement" is described 2 weeks after the first heartbeat, that means at 7 weeks and 2 days of post-menstrual age. One week later, precisely at 8,5 weeks of PMA, we can see the first general movements which are called *fetal or preterm GMs* (gestational age to term to 40 weeks): they are responsible for frequent changes of the position of the fetus in utero, this is an important characteristic of normal fetal motility and is functionally important during prenatal life. The incidence of GMs decreases in the last trimester of pregnancy[(121)]; however, the form of the movement or its "gestalt" remains constant. With preterm birth, there is a continuation of prenatal pattern of movement, and in particular the pattern of GMs which are expressed in a similar way. Very

[b] Visual Gestalt perception is a powerful instrument in the analysis of complex phenomena. In his paper "Gestalt perception as a source of scientific knowledge"(Lorenz, 1971) the Nobel prize laureate Konrad Lorenz pointed out that 'Gestalt perception is able to take into account a greater number of individual details and more relationships between these and any rational calculation'. Visual Gestalt perception is used whenever dynamic or static images are globally assessed. In applying the visual Gestalt perception to the assessment of GMs, the first step is to differentiate between normal GMs and abnormal GMs. If GMs are considered to be abnormal the different age-specific sub-categories are classified as: poor repertoire (PR), cramped-synchronized (CS), abnormal or absent fidgety movements[(126)].

little differences can be observed between fetal and preterm GMs[123]. Thus, the movement repertoire of the newborn is a continuation of that of the fetus[112, 123, 124].

At term age until about 6 to 9 weeks post-term age, GMs are called *writhing movements*[124], characterised by small to moderate amplitude and by slow to moderate speed. Typically, they are ellipsoid in form, which creates the impression of a writhing quality. Fast and large extension movements may occasionally breach through, particularly in the arms (sometimes in this period preterm infants could make abrupt movements). Movements are still variable: it should be hard to predict what will be the next part of the body that is going to be involved by the movement. As the age of the typically developing infant advances, the qualitative characteristic of the movement changes, expressing the developmental changes seen in the young infant's nervous system[112]. At 6 to 9 weeks post-term age, *writhing movements* gradually disappear while *fidgety* GMs gradually emerge[113, 123, 125].

Fidgety movements are small movements of moderate speed and variable acceleration, of neck, trunk and limbs, in all directions, continual in the awake infant, except during focused attention, fussing and crying[124, 125]. They may be seen as early as 6 weeks but usually occur around 9 weeks and are present until 20 weeks[124] or even a few weeks longer, at which time intentional, goal directed, and antigravity movements occur and start to dominate. An early onset of fidgety movements (around 6 weeks) can mainly be observed in infants born preterm[113]. They may be concurrent with other gross movements, such as kicking, wiggling-oscillating and swiping of the arms[126]or pleasure bursts[124, 125] . Initially they occur as isolated events (score: +), gradually increase in frequency (score: ++) and then decrease once again (score:+)[124]. This temporal organization can be defined as:

- *Continual* Fidgety Movements (++): Fidgety movements occur frequently but are interspersed with short pauses. As fidgety movements are by definition GMs, the movements involve the whole body, particularly the neck, trunk, shoulders, wrists, hips and ankles. Depending on the actual body posture, in particular the position of the head, fidgety movements may be expressed differently in different body parts;
- *Intermittent* Fidgety Movements (+): Although fidgety movements occur regularly in all body parts, the temporal organization differs from fidgety movements ++. In fact, the pauses between fidgety movements are prolonged, giving the impression that fidgety movements are present for only half of the observation time;
- *Sporadic* Fidgety Movements: they are like fidgety movement + but with even longer pauses[119].

We can also assess the quality of the fidgety movements: if it is well expressed, we will score it two stars (**), if it is less well expressed, but anyway it is present, we will score it one star (*).

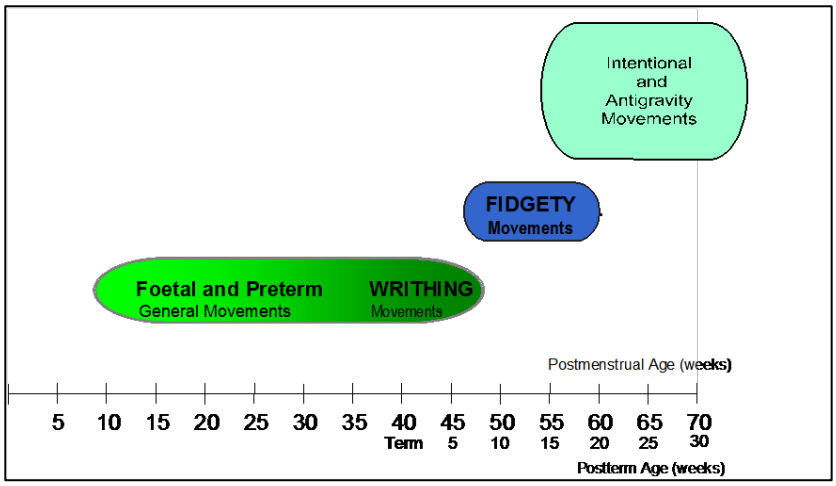


Fig. 2.1 Developmental course of general movements.

2.2 *General movements change their quality if the nervous system is impaired*

The quality of General Movements is probably modulated by more cranial structures (e.g. cortico-spinal, reticulo-spinal) and hence can be affected by impairments of these structures. A disruption of the cortico-spinal projections by periventricular lesions of the corona radiate or internal capsule due to haemorrhages or hypoxic-ischaemic lesions (leukomalacia) leads to abnormal GMs. If the nervous system is impaired, GMs lose their complex and variable character and have a poor repertoire, or are cramped-synchronized or chaotic. This holds true for the preterm, term and early post-term age (first two months). Fidgety movements can be either abnormal or absent[119].

POOR REPERTOIRE GMS

This abnormal GMs pattern occurs during preterm, term and early post-term age. The sequence of the successive movement components is monotonous and movements of different body parts do not occur in the complex way seen in normal GMs [114, 119, 127].

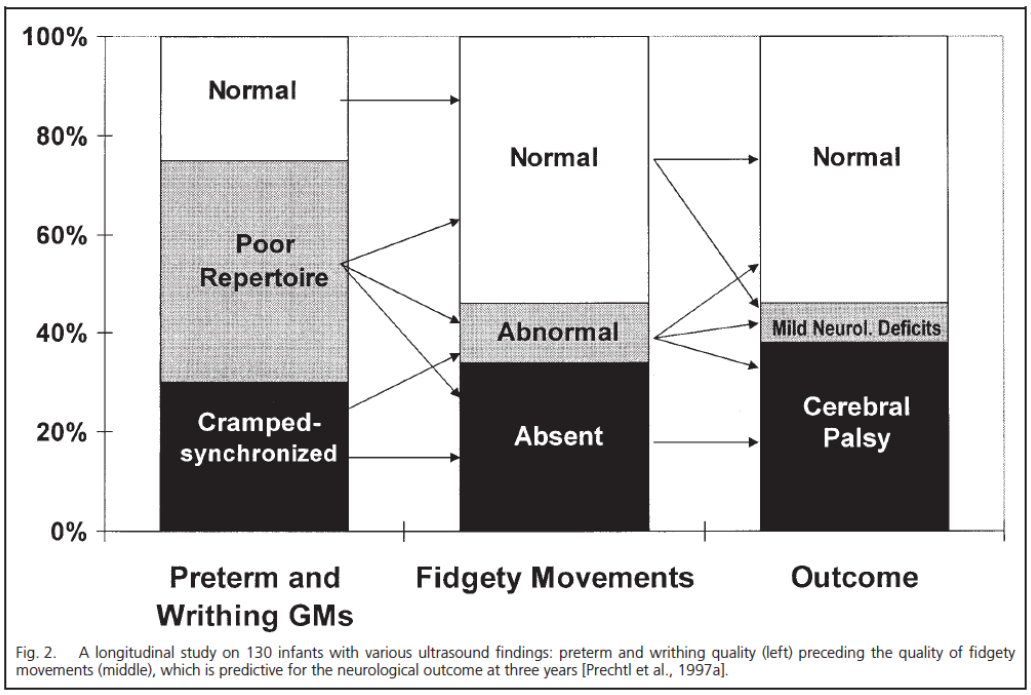


Fig. 2. A longitudinal study on 130 infants with various ultrasound findings: preterm and writhing quality (left) preceding the quality of fidgety movements (middle), which is predictive for the neurological outcome at three years [Prechtl et al., 1997a].

Fig.2.2

Poor repertoire GMs are frequent in infants with brain ultrasound abnormalities, in ELBW[c] infants and during the first two weeks of life. They are unspecific because they could be present also in infants with Down syndrome, Rett syndrome, Dyskinetic CP or inborn error of metabolism. They can be followed by normal, abnormal or absent fidgety movements, hence, the predictive value is rather low[(124)] (**Fig.2.2**). Generally, when GMs showed a consistently poor repertoire, the sequelae were divergent and led not only to relatively mild abnormalities such as attention-deficit hyperactivity disorder (ADHD) and minor neurological disorders (MND) but also to CP.

CRAMPED-SYNCHRONIZED GMS

This is an abnormal pattern from preterm age onwards. Movements appear rigid and lack the normal smooth and fluent character; all limb and trunk mussels contract and relax almost simultaneously[(114, 119, 127)]. If this abnormal pattern is observed consistently over a number of weeks it is of high predictive value for the development of spastic cerebral palsy [(114, 124, 128)].

[c] Extremely Low Birth Weight infants are defined as infants with a birth weight of less than 1000 g.

CHAOTIC GMS

Movements of all limbs are of large amplitude and occur in a chaotic order without any fluency or smoothness. They consistently appear to be abrupt [119, 127, 129, 130]. Chaotic GMs can be observed during preterm, term and early post-term age but are rather rare. Infants with chaotic GMs often develop cramped-synchronized GMs a few weeks later.

ABNORMAL FIDGETY MOVEMENTS

These look like normal fidgety but their amplitude, speed and jerkiness are moderately or greatly exaggerated. Abnormal fidgety movements are rare an their predictive value is low[124](**Fig.2.2**).

ABSENCE OF FIDGETY MOVEMENTS

If fidgety movements are never observed from 9 to 20 weeks post-term we call this abnormality 'absence of fidgety movements'. Other movements can, however, be commonly observed[124]. The absence of fidgety movements is highly predictive for later neurological impairments, particularly for cerebral palsy, both the spastic[124]and dyskinetic forms[131]. (**Fig.2.2**). If the cramped-synchronized is still present at 3 to 4 months (or even longer), fidgety movements are absent (**Table 2**).

Table 2. Characteristics of Abnormal General Movements

Abnormal General Movements	Preterm Age	Term Age	Post-Term Age
Poor repertoire GMs	Monotonous sequence of successive movements without complexity	Continue to appear	Continue to appear Predictive value: rather low
Cramped synchronized GMs	Rigid movements All limb and trunk muscles contract simultaneously	Continue to appear	Continue to appear High predictor for cerebral palsy
Chaotic GMs	Chaotic order of limb movements Large amplitude Abrupt movement Rare	Continue to appear Rare	May develop cramped synchronized movements
Abnormal fidgety movements	No fidgety	No fidgety	8–20 weeks. Exaggerated amplitude, speed jerkiness Predictive value: low to medium
Absence of fidgety movements	No fidgety	No fidgety	9–20 weeks Absence High predictor for neurological impairments

Table 2[132]

Changes in the quality of movements reliably reflected the condition of the brain[133]. This method could therefore be an added tool for the assessment of a challenged neurological system[134].

An important study carried out by Prechtl et al.[124] reported on the predictive value of fidgety movements and neurological outcome at 2 years. Three aspects of GMs were examined: (1) the relationship between abnormal writhing movements and abnormal or absent fidgety movements; (2) normalization of abnormal writhing movements by the fidgety period and its influence on neurodevelopmental outcome; and (3) the effect of abnormal or total absence of fidgety movements on long-term neurodevelopmental outcome. The results suggested that the quality of fidgety movements was directly related to outcome (see *2.5 Cerebral Palsy and GMs*).

These findings were supported by the studies of Bos et al.[129], Hadders-Algra et al.[135] and Cioni et al. [136] who had examined the predictive differences between GMs quality and neurological examination in full-term infants.

2.3 *How to record and assess General Movements*

The simplest way of assessing motor activity is by directly observing the movements with the unaided eye. However, considerable improvement in the reliability of the assessment is achieved if the infant's GMs are observed by replaying a video recording. There is the advantage of repeated playback, including at different speeds, and of storing the recordings for documentation and future reference[119].

RECORDING TECHNIQUE AND PROCEDURE

The video camera should be placed high above the infant. Watching a monitor outside the observation room is a useful way of observing the infant without causing interference. In this way, parents can be asked to soothe their baby if it starts crying because then the recording must be interrupted anyway.[119]

Depending on its age the infant should lie in a supine position in the incubator, bed or on mattress on the floor. The caregiver's presence will not only attract the infant's attention but also interfere with the observer's Gestalt perception. The observer must be able to see the

infant's face to make sure the rigid movements are not due to crying. This is especially important as the later assessment is done without acoustic signals.

A small and non-restrictive nappy is advisable. On very young preterm infants the nappy should be open in order to avoid restriction of leg movements. During the post-term period infants should be dressed lightly and comfortably, leaving arms and legs bare. The room temperature should be comfortable: if the ambient temperature is either too low or too high it will affect the infant's behavioural state and the movement quality.[119]

As GMs are dependent on the behavioural state[112, 127, 137], the movements change during fussing, crying and drowsiness. Therefore, the recording should not be continued during these states. Nor is it possible to judge the quality of GMs properly if the infant is sucking on a dummy. Soothing the infant with a dummy results in the sucking posture (Prechtl and Lenard, 1968) with flexed arms, fisting, and extended legs. In cases of prolonged fussing and crying the recording must be stopped. This may take some time; it may even be necessary to repeat the recording session on another day. However, it should be mentioned that infants with severe brain dysfunction may frequently cry after they start moving, e.g. infants with cramped-synchronized GMs.[119]

Interference by an observer (parent, examiner) and the presence of toys in the immediate vicinity should be avoided. Although we know that spontaneous movements are quite stable and robust and hardly interfered with by stimulation[138], the observer's Gestalt perception might be destroyed by too many distracting objects or persons.

Finally, it is therefore advisable to record GMs during the first three days after birth. During these days, many physiological variables tent to fluctuate more than they do later. There is also an initial instability of behavioural states, changing rapidly from quite sleep to crying, which can interfere with a proper observation of GMs.

The duration of the recording depends on the age of the infant. In order to collect about three GMs for a reliable assessment, preterm infants usually are recorded for 30 to 60 minutes. This does not require the observer's presence during the recording nor the later assessment of the whole recording. From the writhing movement period onwards, five to ten minutes of optimal recording is usually sufficient.

2.4 *GMs and other Neurological Assessments in infancy*

We have different diagnostic tools: Traditional Neurological Examination and Neurodevelopmental tests, electrophysiology, neuroimaging and cognitive, perceptual and behavioural states. Using these tools we want to support the diagnosis, to help define the prognosis, to monitor the longitudinal history of the disease and to document the effects of interventions.

The first thing that has been done when the general movements assessment was developed was to compare this with the state of the art at that time. All the first studies made by the fist scientists using GMs wanted to compare this new method with the neurological examination and it is not surprising that they found similar results in sensitivity and specificity, although overall GMs was confirmed to be a bit higher in predictive power. This has be underlined by recent meta-analysis, which added also that at 3 months of age GMs are the most powerful clinical tool that we have to predict the neurological outcome.

GMs and Neurological Examination

The introduction of sophisticated neuroimaging techniques has supplemented but not replaced the neurological examination (NE) of the newborn. The information provided by this examination is still very important for a rapid diagnosis of a neurological disorder in a newborn, for deciding on the need for and type of imaging, electrophysiological or other examinations to be carried out, for formulating a prognosis and for monitoring, by repeated checks, the developmental disorder[(136)].

The classical NE explores the newborn's aspects like posture, tone, movements, reflexes and behaviour. One of the most used currently is the Dubowitz examination[d].

The problems related to the NE are that it is based on reflexes, many items are too intrusive for babies (especially for preterm infants) and the predictive power is lower than other approaches (there are false positives and false negatives).

[d] Dubowitz examination is a method of clinical assessment of gestational age in the newborn that includes 10 neurologic criteria (as posture, ankle dorsiflexion, arm recoil, leg recoil, popliteal angle etc.) for the infant's maturity and 12 physical criteria (as edema, skin texture, skin colour, skin opacity, lanugo etc.) to determine the gestational age of the infant. It is useful from birth to 5 days of life. The Dubowitz global score can be from 0 to 72 (neurological signs 35, external signs 37) and the estimated gestational age is obtained in this way: (0.2642 * (total score))+24,595.

The preterm infant: Preterm infants are generally submitted to a neurological examination in the neonatal period, with the aim of assessing the functional consequences of brain lesion, which may have been found by neuroimaging, and to predict long-term neurological outcome. It is always preferable to use a comprehensive, structured and standardised neurological examination than a random selection of items. Standardised and validated protocols permit testing the different subsystems of the neonatal nervous system. For the preterm period the protocol by Dubowitz and Dubowitz is available even if it is difficult to apply some of the Dubowitz items to fragile preterm [139] and the predictive values are rather low[140, 141].

In a comparative study on 66 preterm infants with various brain ultrasound findings (from normal to grade 3 intraventricular haemorrhage and periventricular leukomalacia) the percentage of agreement (normal versus abnormal) between GM assessment and neurological examination during the preterm period was quite low, namely 73%. As these infants were repeatedly examined, the percentage of agreement constantly increased, reaching 92,6% at the 4- to 5-month-examination. Overall agreement was 80%[139].

The sensitivity of the GM assessment is very high at all ages but the specificity is low during the preterm, term and early post-term period. This is due to a consistent number of infants with abnormal GMs who normalise during the fidgety movement period and have a normal outcome. Thus, specificity only becomes high at 3 to 4 months.[119]

The sensitivity of the neurological examination is quite low at preterm and term age, because of infants with apparently normal findings during their neurological examination who develop cerebral palsy. The specificity is low until 4 months.[119]

A four-centre study on preterm infants with unilateral intraparenchymal echodensity replicated also the superior predictive power of longitudinal GM assessment. Particularly at preterm and term age, neurological examination had a higher number of false-negatives and false-positives for the neurological outcome than the GM assessment. Moreover, the three cases with unilateral intraparenchymal echodensity who did not develop hemiplegia had normal fidgety movements, although one of them had abnormal findings at the neurological examination, i.e. hypertonia and asymmetry[142].

The full-term infant: A first comparison between GM assessment and neurological examination in full-term infants with hypoxic-ischaemic encephalopathy indicated a slightly higher prognostic value of GM assessment in the first two weeks post-term and of neurological examination at about 5 to 6 months[143].

The first systematic comparison was carried out on 58 infants[136] representing uneventful obstetrical and neonatal histories as well as hypoxic-ischaemic encephalopathy of various degrees. The neurological examination at the various ages [144-146] resulted in more abnormal findings than did the GM assessment. The overall percentage of agreement was 81% and thus similar to that in preterm infants. GM assessment and NE had good sensitivity values, slightly better for the former at all age periods. Specificity was low for both techniques at term age, because some subjects with poor repertoire GMs or mild neurological abnormalities at that age were normal at 2 years. At 2 months post-term the specificity for the GM assessment was good and already superior to the NE. According to these data, normalisation of transient disorders might be assessed earlier by GM observation.[139]

GMs, BRAIN ULTRASOUND AND NEUROIMAGING

Studies on the relationship between ultrasound findings, developmental trajectories and neurological outcome revealed the GM assessment to be superior to ultrasound findings. Of course, GM assessment can never replace neuroimaging techniques but it is a worthwhile method to be used in combination with neuroimaging.

Traditional NE, assessment of GMs and neuroimaging are tools targeting different aspects of the neurological development: the traditional NE is more targeted to assess the impairment, while the GMs are more related to functional limitations and neuroimaging is more targeted to the pathogenesis. They should be used all together to rich the best predictive power.

2.5 *Cerebral Palsy and GMs*

Cerebral Palsy (CP) is a well-recognized neurodevelopmental condition that starts to manifest early in childhood, usually before 18 months of age[147]. It is an 'umbrella term' that refers to a group of disorders affecting a person's ability to move, it is a permanent life-long condition, but generally does not worsen over time.[e]

[e] "*Cerebral Palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbance that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbance sensation, perception, cognition, communication, and behaviour,*

The prevalence of CP increases with the decreasing gestational age from 0,1% in children born at term to 14,6% in children born below 28 weeks of gestational age[148, 149]. Spastic CP is the most common form of CP in children born preterm, whereas in children born at term, non spastic forms predominate[148]. Bilateral spastic CP is more widespread than unilateral spastic CP both in children born preterm (73 vs 21%) and born at term (48,5 vs 36,5%)[148].

In Italy CP has an incidence of 1000 new cases per year, every 8 hours a newborn who is going to develop cerebral palsy born and today there are more than 100000 infants, children and adults affected by CP.

One of the most challenging tasks for medical practitioners is to identify specific risk factors in early infancy and predict severe impairment that manifests later in development.

It is important to note that in many people the cause of CP remains unknown, however the most frequent causes of CP can be divided as *prenatal*, *perinatal* and *postnatal*:

- *Prenatal causes* include genetic disorders, malformations, infections, abnormal intrauterine growth and hypoxic-ischaemic lesions;
- *Perinatal causes* (from 48h before birth until 7 days of postnatal life) include asphyxia, intracerebral haemorrhages and CNS infections (predominant in preterm infants);
- *Postnatal causes* (the first three years of life) include seizures, vascular events mostly resulting in hemiplegia.

The parents, on their part, are all the more anxious to learn about the developmental perspectives of their infant, especially if the infant has an adverse perinatal history. On the same time, one should consider that overt clinical symptoms of CP usually do not emerge before the child is at least half a year old[147, 150]. In addition to the low gestational age and low birth weight, perinatal asphyxia and neonatal encephalopathy, white matter disease, severe intraventricular haemorrhage, cerebral infarction, deep grey matter lesions, infections and multiple genetic factors have been identified as risk factors for CP[151-153].

The result of the studies on cohort of infants with CP suggests that consistently cramped-synchronized GMs were highly predictive of severe neurological problems. In fact, in certain cases, the presence of these abnormal GMs occurred long before clinical signs of CP become evident. The earlier the abnormal GMs are observed, that is, when already present in the preterm stage, the worse will be the later impairment[114]. The evidence also showed that when

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by epilepsy and by secondary musculoskeletal problems."[147] This is the definition of CP given by the Executive Committee during an international workshop in Bethesda, MD (USA) on July 11-13, 2004.

cramped-synchronized GMs expressed in the writhing period are found together with the absence of fidgety movements, probability of the development of spastic type CP increased[131].

In 1997, Heinz Prechtl and associates proved the assessment of GMs, particularly during 3-5 months of age, to be a reliable and valid tool for distinguishing between infants who are at significant risk of developing CP and infants who are not[124]. The findings were based on a longitudinal study on 130 infants who represented the whole spectrum of perinatal brain ultrasound findings. Central to the study were the age-specific fidgety movements. It was found that 96% of infants with normal fidgety movements (n=70) had a normal neurological outcome. Abnormal quality or total absence of fidgety movements was followed by neurological abnormalities (most of them CP) in 95% of the 60 infants. Specificity and sensitivity[f] of the assessment of fidgety movements (96 and 95% respectively) were higher than of cranial ultrasound (83 an 80% respectively)[124].

The mere absence of fidgety movements, however, cannot predict the subtype or the severity of CP. This fact indicates that intact cortico-spinal fibers and a normal output of the basal ganglia and cerebellum are necessary to generate normal fidgety movements[154]. Magnetic resonance studies have demonstrated that in very preterm infants, white matter lesions[155]and a reduced cerebellar diameter[156] were associated with absent fidgety movements.

In infants born at term, the severity of the injury to the central grey matter correlated with a lack of fidgety movements[157] . Interestingly, fidgety movements were also absent in infants with genetic disorders like Rett syndrome and its preserved speech variant[158-160], Smith-Magenis syndrome[161], as well as in infants with autistic spectrum disorders[162].

After discovering fidgety movements as an age-specific, distinct form of GMs, Prechtl contemplated the potential biological function of this transient movement pattern[163]. He hypothesized that one of the ontogenetic adaptive functions of these small movements is optimal calibration of the proprioceptive system. This assumption in supported by the fact that fidgety movements emerge during the transformation of neural functions at three months

[f] Sensitivity is the number who are both disease positive and test positive divided by the number who are disease positive; it is the percentage of cases which are correctly identified as high-risk for later neurological impairment[175].

Specificity is the number who are both disease negative and test negative divided by the number who are disease negative; it is the percentage of cases which are correctly identified as normal[175].

of age[164]and therefore precede the onset of intentional reaching or visually controlled manipulation of objects[163, 165]. Since in many respects adaptation to the extrauterine condition is not completed before the third month post-term[166], the proprioceptive system is still matched to the intrauterine environment. A recalibration of the sensory system is required in order for fine motor skills to develop properly[163].

If we look at the developmental trajectories[g], (**Table 2.1**), we can observe that abnormal fidgety movements are preceded by abnormal writhing GMs: Cramped-synchronized are highly predictive (98%) for the eventual development of spastic CP.

We speak about "abnormal fidgety movements" but, is there any difference between *sporadic* fidgety movements and *absent* fidgety movements? A recent longitudinal study by Einspieler et al.[167] had the objective to determine whether infants who had developed CP and had sporadic fidgety movements have a better outcome than infants who did not have fidgety movements. The study comprised 61 children who developed CP (46 male, 15 female; 29 infants born preterm), videoed for the assessment of movements and postures at 9 to 16 weeks post-term age. The conclusion of this study was that there were no evidence that the occurrence of occasional isolated fidgety bursts indicates a milder type of CP[167].

Table 1. Developmental trajectories with a high predictive power for normal development and the development of cerebral palsy.

GMs during preterm age	Writhing GMs (at term until 8 weeks post-term)	Fidgety GMs (3–5 months)	Neurological outcome	Ref.
Poor repertoire or normal GMs	Poor repertoire or normal GMs	Normal fidgety movements	Normal	[8–10,14,15,27,36,42,50,51]
Poor repertoire or cramped-synchronized GMs	Cramped-synchronized GMs	Absence of fidgety movements; abnormal findings in neurological examination	Bilateral spastic CP	[4,8–10,15,17,22,24,27–30, 36,42,44,50–55,58–64]
Poor repertoire or cramped-synchronized GMs	Poor repertoire or cramped-synchronized GMs	Absence of fidgety movements and asymmetrical segmental movements; normal or abnormal findings in neurological examination	Unilateral spastic CP	[15,17,45–47]
Poor repertoire GMs	Poor repertoire GMs; circular arm movements and finger spreading	Absence of fidgety movements; absence of foot-to-foot contact; circular arm movements and finger spreading	Dyskinetic CP	[15,48]

CP: Cerebral palsy; GM: General movement.
Adapted with permission from [16].

Table 2.1[168]

g When the quality of GMs is repeatedly assessed during the preterm, term and postterm period until about 20 weeks, an individual **developmental trajectory** can be obtained indicating the consistency or inconsistency of normal or abnormal findings (Prechtl 1990). An individual developmental trajectory should document the following GM assessments: two to three recordings of preterm period (three GMs sequence each); one recording at term or early postterm age or both; at least one recording between 9 and 15 weeks postterm. If an absence of fidgety movements is found the infant should be recorded a second time during the fidgety movement period, e.g. at 12 and 15 weeks postterm age[126].

2.6 *Can we identify a high risk for unilateral CP by means of observation?*

Children with unilateral spastic CP showed abnormal (usually cramped-synchronized) GMs during their first week of life; moreover, they had no fidgety movements at 3-5 months post-term age, a circumstance that refuted the hypothesis of a *silent period* of unilateral CP[142]. At the age of 2-4 months the first asymmetries could be observed: contralateral to the side of the lesion and regardless of the position of the head, the so-called "segmental movements" (i.e., distinct movements of hand and feet, fingers and toes, occurring either isolated or as a parte of GMs) were reduced or even absent[142, 169]. At this age, neurological examination might still yield normal results (**Table 2.1**).

The combination of the Hammersmith Infant Neurological Examination (HINE)[h] with the assessment of GMs facilitated early identification of unilateral CP[170]. In an Italian multicentre study, 13 children out of 903 preterm infants were eventually diagnosed with unilateral CP. Eleven of them had no fidgety movements. This findings is especially remarkable since nine of the infants had had a persistent flare on the brain ultrasound with no signs of unilateral damage, meaning that their brain ultrasound had not pointed to later unilateral or any other form of CP. Surprisingly, the HINE scores of all but one infants were within the normal range[170]. These results clearly lead to the conclusion that a 3-4 month-old infant with a normal neurological score but an absence of fidgety movements and asymmetric segmental movements is at a high risk of developing CP[171].

Guzzetta et al.[172]have also explored the predictive value of qualitative assessment of hand movements in 3-month-old infants after neonatal stroke. Their study enrolled 13 infants born at term, 5 females and 8 males, with neonatal AIS and 13 healthy infants. The absolute frequency and the asymmetry of global hand opening and closing, wrist segmental movements and independent digit movements were assessed from videotapes recorded around 12 weeks.
Five of the 13 infants with neonatal stroke had normal neurological development and 8 had hemiplegia. Asymmetry of wrist segmental movements and the absolute frequency of independent digit movements were significantly different between infants with and without

[h] Hammersmith Infant Neurological Examination (HINE): it is a neurological examination for infants between 2 to 24 months. It contains 26 items assessing cranial nerve function, posture, movements, tone and reflexes; each item gives a score, the global score can range between 0 and 78.

hemiplegia. No differences were found in global hand movements. The results confirmed a significant correlation between asymmetry of wrist movements at 3 months after birth and the presence of later hemiplegia in infants with neonatal stroke[169].

2.6.1 *Is it possible to differentiate between later spastic diplegia an tetraplegia?*

Consistent cramped-synchronized GMs predict both spastic diplegia and tetraplegia. Cases with later diplegia had a later onset and shorter duration of cramped-synchronized GMs than cases with later tetraplegia[128]. If in addition to the cramped-synchronized GMs so-called segmental movements were frequently present in the upper limbs, the child most probably developed diplegia[173].

2.6.2 *Are there markers for dyskinetic CP?*

Einspieler et al.[131]found that dyskinetic CP correlated well with poor repertoire of GMs. Movements in these infants were monotonously slow and accompanied by abnormal upper limb movements that were characterized by stereotyped circular arm movements and finger spreading (**Table 2.1**). Usually, these abnormal movements remain until at least 5 months post-term. A lack of movements towards the midline, particularly foot-foot contact, is an additional specific sign of later dyskinetic cases. Common to both spastic and dyskinetic cases was the absence of fidgety movements and the absence of antigravity movement, i.e. leg lifting, during the third to fifth month[119].

2.7 *GMs as early markers for CP*

The methodological breakthrough of the GM assessment, which is nonintrusive, easy to acquire and cost effective[119], lies in its predictive value of the development of neurological deficits, in particular of CP, at a much earlier age than before[124]. Recognition of abnormal GMs can help to improve earlier detection of CP if this technique is successfully incorporated into follow-up programs and developmental surveillance[174]. A number of studies have proposed to combine the GM assessment with neuroimaging, especially MRI, and/or a

neurological assessment as such a combination is even more effective in predicting the neurological outcome than the GM assessment alone.[136, 139, 155-157, 171, 175-179]

The great advantage of detecting an increased risk of CP at such an early stage consists of the possibility of intervention long before the emergence of obvious pathological features of CP. The consistent presence of cramped-synchronized GMs, and even more so the absence of fidgety movements, puts an infant at such a high risk of CP, that physiotherapeutic intervention is justified. Furthermore, it is no less important to identify infants who, despite an increased risk based on their clinical history, have normal GMs and can thus be expected to have a normal neurological outcome[168]. Even though there is actually no proof that early intervention could prevent CP, it may have a positive effect on the quality of spontaneous movements and hence, the child's functional abilities in the future[133, 174, 180].

To quote from Prechtl and his colleagues:

"Our technique of assessing spontaneous motor activity can identify and distinguish between those infants who require early intervention for neurological abnormalities and those who do not"[139].

2.8 *The GMs Trust*

Since the standardization of Prechtl's method of assessment the quality of GMs in the early 1990s, a large number of articles have been published by Prechtl and his co-workers to establish the integrity of this assessment and its predictive validity (e.g. Cioni et al. 1997[139]; Hadders-Algra et al. 1997[135]; Prechtl et al. 1997[124]).

Together with Prechtl, researchers Cioni, Ferrari, Hadders-Algra, Einspieler and Bos did the pioneer studies of GMs[134]and established *the GMs Trust* in 1997.

The GMs Trust was founded in order to provide standardized training for doctors and therapists working in the field of infant neurology. Participants come from around the world to The Netherlands, Austria and Italy for training in GMs assessment. This is required for a proper application of this objective, reliable and valid method.

To examine the effectiveness of the 4-day standardized training course, 700 scoring sheets (containing a total of 8019 assessments) from the final tests of 18 courses were evaluated: 83% of the assessments correctly observed the GMs movements quality, whereas 92% could discriminate between normal and abnormal GMs[181]. Nevertheless, a certain bias arises from the fact that most of the studies by the Prechtl group were carried out in The Netherlands an

Italy, with some of those based on the same samples. This is particularly relevant with respect to the preterm population that consist mainly of high-risk neonates suffering from physical disability an therefore not entirely representative of preterm infants in general[132].

2.9 *Cautions and limitations*

For the assessment of GMs any kind of environmental stimulation may interfere with the observer's Gestalt perception and should be avoided.

Because tiredness certainly interferes with the visual Gestalt perception, the observer should never assess for longer episodes than about 45 minutes without taking a break[119, 127]. If many recordings of abnormal GMs are observed in a series, one is advised to watch a gold standard normal recording[119, 125] from time to time. This is necessary for re-calibrating the Gestalt perception.

A serious concern that has been raised is whether a systemic disease, such as infection without brain involvement (*Candida* species, coagulase-negative *Staphylococcus*, *Staphylococcus aureus*), might mimic an impairment of GM quality similar to those in brain dysfunction.[180] Bos and co-workers[129] demonstrated that septicaemia has a limited influence on the GM quality. At first notice, the GM in infants with septicaemia could be mistaken for GMs with poor repertoire. However, the richness in complexity and variability, in particular of the sequence of the moving body parts, including superimposed rotations, was strictly different from truly poor repertoire GMs. GMs of preterm infants with severe infection have just a sluggish character with a slow speed. Hence, it is possible to discriminate between abnormal GMs due to brain lesions and sluggish GMs due to a severe systemic infection, when the complexity of the GMs is considered as the main characteristic for normal GMs.[182]

For the less-experienced observer, it might be sometimes difficult to distinguish between abnormal GMs and seizures. GMs with a poor repertoire show a monotonous sequence of the successive movements components that recall stereotyped movements of subtle seizures. Similarly, cramped-synchronized GMs may resemble tonic posturing of focal or generalized tonic seizures. What is peculiar to seizure movements but certainly not to abnormal GMs are the extreme stereotypy and the ictal character of the clinical phenomena. The sequence of movements does not change during the single seizure or even in successive seizures. Abnormal GMs are monotonous in the sequence but are never stereotyped to such a degree

that seizures are. Other ictal motor phenomena, such as abnormal eye movements or oral-buccal-lingual movements or autonomic phenomena during limb movements, are never seen during poor repertoire or cramped-synchronized GMs[119]. If the clinical observation does not provide a differentiation between seizure and abnormal GMs, an EEG-recording can be helpful despite not all motor automatism and particularly tonic generalized seizures are consistently accompanied by epileptic discharges in the EEG.[180]

2.10 *Strengths and benefits*

The methodological breakthrough of this assessment technique lies in the fact that it predicts the later development of CP at a much earlier age than was previously possible. In addition, the qualitative assessment of GMs is totally non-intrusive, easily learned, and cost-effective. The great advantage of being able to detect the risk of later development of CP so early is the possibility to install interventions long before pathological features of CP develop. It is most unlikely that these interventions will prevent the development of CP, but they can help prevent secondary defects such as contractures and other forms of immobility. Thus, GMs are going to be integrated in the new guidelines of the early detection of cerebral palsy.

The psychological support for parents and the maximal functional deployment and early adaptation of the impaired child are of crucial importance. In addition, it is of similar significance to select those infants with normal GMs who, despite being at risk because their history, will have a normal neurological outcome[180].

Chapter 3

EXPERIMENTAL STUDY

3.1 Aims of the study

The general aim of our study was to confirm or reject the hypothesis of a *silent period* that would prevent an early identification of unilateral CP. More specifically our aims were (1) to analyse to what extent the motor performance at age 3 to 5 months was associated with the long-term neurological outcome; (2) to confirm the predictive power of fidgety movements; (3) to confirm the significant correlation between an asymmetry of segmental movements and the presence of later hemiplegia in infants with neonatal stroke; (4) to investigate whether infants with a later diagnosis of hemiplegia have more often asymmetries in their hand movements, kicking, trunk bending and foot-foot contact.

3.2 Method

3.2.1 *Participants*

The study comprised 22 infants; 16 infants with a neonatal stroke (14 males and two females) and six healthy infants (five males and one female) with typical development serving as controls. All infants were born at term with a gestational age ≥ 37 weeks. They were born between February 2009 and June 2012 in or near Columbus, OH, USA.

Some of the individuals participated in a previous study by Chen et al.[183] with the aim to investigate an association between neonatal stroke and movements towards the midline, as well as, fine and gross motor behaviours.

Some infants with neonatal stroke had been admitted to the Stroke Clinic at Nationwide Children Hospital (Columbus, OH) with clinical signs of stroke including seizures and

weakness; some others were recruited by word of mouth. Healthy infants and infants with neonatal stroke did not differ in baseline characteristics, such as gestational age and birth weight (independent sample t-Test, respectively p=0.91 and p=0.50; **Table 3.1**). Neonatal stroke was confirmed by MRI.

Inclusion criteria for the study were:

- Gestational age at birth ≥ 37 completed weeks;

- Neonatal cerebral infarction observed on neuroimaging;

- At least one but preferable sequential video-recordings at the age of 3 to 5 months, which could be used to assess GMs;

- Neurological follow-up available.

Infant	Gender	GA (wks)	BW	Group	Side of Stroke	Motor Outcome
1	Male	40	3005	Stroke	L	CP - R spastic hemiplegia
2	Female	39	3061	Stroke	L	CP - R spastic hemiplegia
3	Male	40	3515	Stroke	L > R	CP - R spastic hemiplegia
4	Male	39	3203	Stroke	L > R	Mild R UE hemiparesis
5	Male	36	3061	Stroke	/	Myotonic Dystrophy
6	Male	39	3175	Stroke	Bilateral	Average Bayley-III at 18 months
7	Male	38	3203	Stroke	R > L	Average Bayley-III at 18 months
8	Male	39	2920	Stroke	L	Average Bayley-III at 11 months
9	Male	41	3231	Stroke	R	Average Bayley-III at 8 months
10	Male	41	3742	Stroke	R	TD assumed
11	Female	39	3515	Stroke	L	TD assumed
12	Male	39	3657	Stroke	Bilateral	TD assumed
13	Male	39	4450	Stroke	Bilateral	TD assumed
14	Male	38	3090	Stroke	Bilateral	TD assumed
15	Male	36	2126	Stroke	R	/
16	Male	37	2608	Stroke	R	/
17	Female	39	3260	Control	NA	Typically Developing
18	Male	/	/	Control	NA	Typically Developing
19	Male	38	2835	Control	NA	Typically Developing
20	Male	38	3345	Control	NA	Typically Developing
21	Male	40	/	Control	NA	Typically Developing
22	Male	40	/	Control	NA	Typically Developing

Key: GA (Gestational Age); BW (Birth Weight in grams); L (left); R (right); CP (Cerebral Palsy); UE (Upper- Extremity); TD (typical development); / (data not available); NA (not applicable).

Table 3.1

Video recordings in which infants were crying, fussing, sucking on a dummy or distracted by their immediate surroundings had to be excluded.

As we do not know the outcomes of Cases 15 and 16, we excluded them from the final sample. Also case 12 was excluded because his video-recordings did not permit reliable assessment.

The final cohort consisted of 19 infants, 16 males and 3 females.

3.2.2 *Video-recordings*

The video camera was positioned to the left side of the infant with 30° away from the midline and at 1.2 m height.

All infants were video-recorded from 2 to 7 months of age, but for the purpose of our study we only selected videos from 9 to 20 weeks post-term age, in order to reliably assess the absence or presence of fidgety movements. There was a minimum of one to at least ten video-recordings for each infant (median = 6). Infants were recorded in supine position either without manipulation (baseline), or for the purpose to elicit movements to the midline[183] by placing various toys into the hand.

As our aim was to assess the spontaneous motility of the infants, we selected those clips in which the infant was neither manipulated by a caregiver nor manipulated him/herself any objects. The duration of each clip for the assessment of spontaneous motility was at least 60s for each evaluation.

We divided the video-recordings into six age-sessions, according to the post-term age:

T1: 9-10 weeks

T2: 11-12 weeks

T3: 13-14 weeks

T4: 15-16 weeks

T5: 17-18 weeks

T6: 19-20 weeks

Table 3.2 provides how often an infant was assessed for the aim of the present study.

		Age groups					
Infant	**Group**	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**
1	Stroke	-	x	-	-	-	-
2	Stroke	x	x	-	-	-	x
3	Stroke	x	x	-	-	x	-
4	Stroke	-	x	-	-	-	-
5	Stroke	-	-	-	-	-	x
6	Stroke	-	x	x	-	x	x
7	Stroke	-	-	-	x	-	-
8	Stroke	x	x	x	x	x	-
9	Stroke	-	x	x	-	x	x
10	Stroke	x	x	x	x	x	-
11	Stroke	-	-	x	x	-	-
13	Stroke	x	x	x	x	-	x
14	Stroke	-	-	x	-	-	-
17	Control	x	x	-	x	-	-
18	Control	-	x	x	-	x	x
19	Control	-	x	x	x	x	-
20	Control	-	-	-	x	-	x
21	Control	x	x	x	x	x	x
22	Control	-	x	x	x	x	x

Available video-recordings for each case across age-groups.

Table 3.2

3.2.3 *Assessment of Motor Repertoire*

For each infant we used the score sheet for the assessment of Motor Repertoire[119] in order to calculate a motor optimality score (MOS) from 3 to 5 months of age. The score sheet comprised the following five subcategories:

1. *Fidgety movements* were classified as normal (12 points); abnormal (i.e. exaggerated, with excessive amplitude, speed and jerkiness; 4 points); or absent/sporadic (1 point);
2. An *age-adequate motor repertoire* scored 4 points (e.g. swipes, wiggling-oscillating, kicking, excitement bursts, smiles, mouth movements, head rotations, hand-mouth contact, hand-hand contact, fiddling, foot-foot contact, legs lift, hand-knee contact, arching, rolling to side, visual scanning, hand regard, head anteflexion). A *reduced* repertoire

scored 2 points if: 1) at 12 weeks foot-foot contact was missing, 2) at 14 weeks there was no hand-hand contact and 3) at 16 weeks the infant had no legs lift. If the infant showed a very poor pattern or lacked the developmental milestones at different ages (e.g. at 14 months the infant had no hand-hand contact, neither foot-foot contact) we scored as *absent* (1 point);

3. The *quality of the movement patterns* (other than fidgety movements): each of the above mentioned movement patterns can have a normal or abnormal appearance. We assessed only the patterns we were able to see in the video-recordings. If normal movement patterns were more than abnormal the score was 4, an even number of normal and abnormal movement patterns scored 2 points; predominantly abnormal patterns scored 1 point;
4. The *observed postural patterns* were scored 4 points if normal patterns (of head, trunk, fingers and limbs) prevailed. As with the quality of movement pattern, an even number of normal and abnormal postural patterns scored 2; 1 point was given if abnormal patterns predominated[184];
5. The *overall quality of motor repertoire* was considered normal if all movements gave the impression of smoothness and fluency (4 points); jerkiness, monotony, tremors and absence of variability in speed and amplitude were rated as abnormal (2 points); 1 point for a cramped-synchronized pattern (rigid movements, limb and trunk muscles contracting and relaxing almost simultaneously).

The motor optimality score ranges from maximum 28 (the best performance possible) to a minimum value of 5.

As not all items could be assessed for each infant, we will report the Motor Optimality Score as percentage of the maximum obtainable score.

3.2.4 *Assessment of Asymmetries*

New evidence suggests that spontaneous hand and digit movements in infants from birth to 5 months are various and abundant, including segmental wrist movements, global opening and closing of the hand, independent finger movements, pre-precision grips (sideway contact

between thumb pad and the side of other fingers), and precision grips (contact between thumb pad and other digits pads)[185]. The emergence and early development of some of these complex movement patterns has been proposed to be related to the maturation of the cortico-spinal tract, based on recent electrophysiological and anatomical studies, suggesting that, in humans, direct connections of the corticospinal tract to motor neuron are established before birth[186].

In 2003, a study by Guzzetta et al.[169] has shown that GMs detect early signs of hemiplegia in term infants with neonatal cerebral infarction. One of the aims of their study was to evaluate the presence of early movement asymmetries and they found that a reduction of segmental movements on one side of the body was observed in all but one of the infants with infarctions and was also correlated with later hemiplegia.

In 2009, Guzzetta et al.[172] explored the predictive value of quantitative assessment of hand movements in 3-month-old infants after neonatal stroke. They found that asymmetry of wrist segmental movements and the absolute frequency of independent digit movements were significantly different between infants with and without hemiplegia ($p=0.006$ and $p=0.008$ respectively), while no differences were found in global hand movements.

We therefore performed a detailed qualitative analysis of (1) single fingers movements, (2) segmental movements at the wrists, but also of (3) global hand movements, (4) kicking, (5) trunk bending, (6) foot-foot contact and (7) head position (right, left or centred). Independent digit movements include all of the digit movements such as isolated movement of one finger, simultaneous movement of two or more fingers and sequential movement of two or more fingers; segmental movements of the wrist were movements of moderate speed at the level of the wrist joint, including rotations, palmar flexion an extension, and ulnar or radial flection; global hand movements were the simultaneous flexion (closing) or extension (opening) of all the digits towards or away from the palm; kicking was defined as flexion-extensions of the legs of minimum three times in a row; trunk bending was defined as an asymmetrical trunk position, whereas the imaginary line between both shoulder joints and the imaginary line between the hip joints were not parallel and we indicated the "concave" side of the trunk; when the foot-foot contact was present but it was abnormal we defined which was the foot consistently supported the other.

We assessed asymmetries for all six age-groups (T1-T6).

Each video-recording was assessed by at least two independent observers (GV, SS, CE, AG). None of the observers was aware of the clinical history or the outcome during the assessment procedure. 10% of all videos were used to calculate inter-observer agreement. A Cohen kappa of 0.86 indicates excellent agreement.

3.2.5 *The neurodevelopmental outcome of the study cases*

On the basis of the neurological outcome we grouped (a) control infants (*normal*), (b) infants with neonatal stroke and a rather normal neurological outcome (*mild*) and infants with neonatal stroke and an adverse neurological outcome, such as right spastic hemiplegia (*adverse*).

The *normal group* contained six healthy infants, one female and five males, with a typical development; the *mild group* included eight stroke infants, one female and seven males, whose outcome was inconspicuous during the second year of life, with age-adequate score at the Bayley Scales of Infant Development, 3rd edition (Bayley-III) at 8, 11 or 18 months; the *adverse group* consisted of five stroke infants, one female and four males later developing right spastic hemiplegia or mild right hemiparesis of the upper extremity. We also included in the last group an infant (Case 5) later diagnosed with myotonic dystrophy, a genetical disease characterized by wasting of the muscles, cataracts, heart conduction defects, endocrine changes, and myotonia.

3.2.6 *Statistics*

SPSS Version 22.0 was used for the statistical analysis.

As the samples were smalls and the variables (except birth weight and gestational age) not normally distributed, non-parametric tests were used. Fisher's Exact test was applied to compare nominal data (e.g. group x fidgety movements). The Mann-Whitney-U test was applied to compare two groups with regard to one dependent outcome variable (e.g. motor optimality score). The Kruskal-Wallis test by ranks was applied to test whether three independent samples (i.e. three groups) originate from the same distribution. The Independent Samples T-test was used to compare whether two groups (stroke vs. controls) had different average values of birth weight and gestational age.

3.3 Results

3.3.1 *The Assessment of the Motor Repertoire*

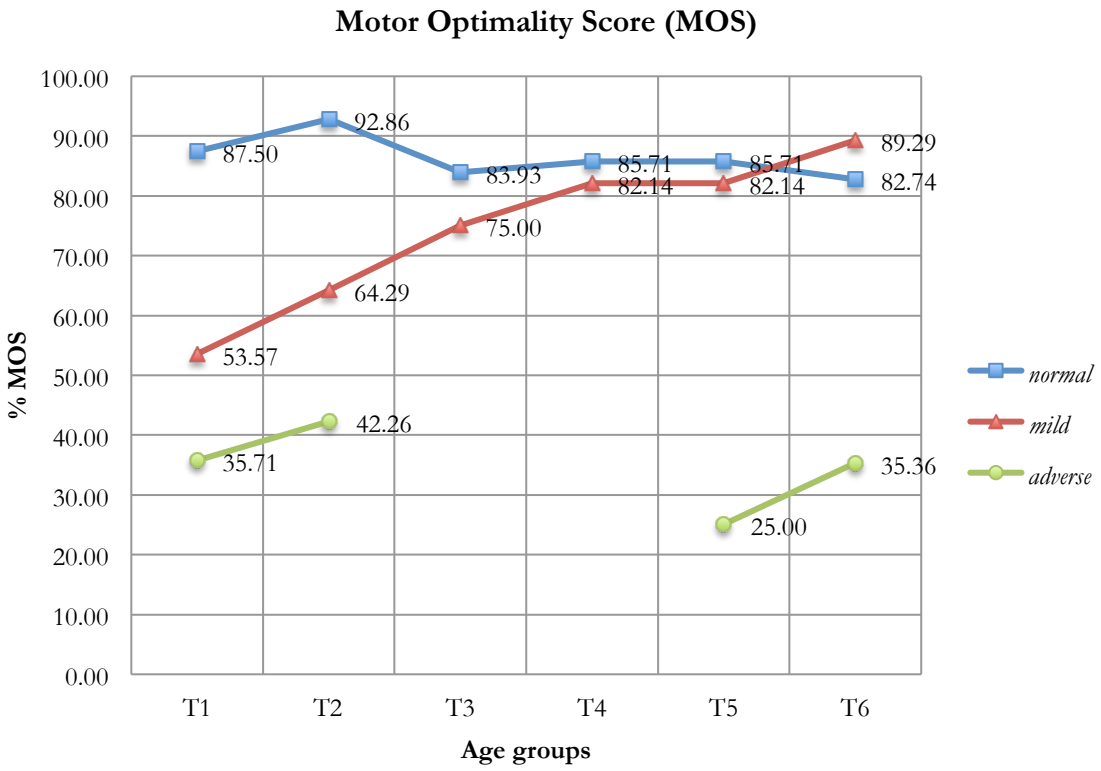
The motor optimality score ranges from maximum 28 (the best performance possible) to a minimum value of 5. For two of our participants the maximum score reachable was 12, because we were not able to assess two of the five subcategories (*fidgety movements* and *overall movement character*). For another infant the maximum score reachable was 16 because *fidgety movements* were not assessable and for, again, another infant it was 20 instead of 28 because the *quality of the movement patterns* and the *global movement character* were not assessable. For this reason we calculated the overall Motor Optimality Score as a percentage of the maximum score reachable by each infant.

As indicated in **Table 3.2** and **Fig.3.1** not all infants were recorded in each age-period. We therefore assigned an average "overall MOS across ages" to each infant. **Table 3.3,** left column, provides the group differences (median and range) between these overall MOSs demonstrating that infants with an adverse outcome scored lowest whereas infants with a normal outcome scored highest (Kruskal Wallis Test, $p<0.05$; see also **Fig.3.1**). If we merged *normal* and *mild* and compared their overall MOS with the *adverse* group the difference was even more pronounced (Mann-Whitney-U Test, $p=0.01$).

Groups		MOS across ages	Subcategory 2	Subcategory 3	Subcategory 4
normal n=6	Median	84%	2	4	3,5
	Range	63-95%	1.4-4	4-4	1.5-4
mild n=8	Median	70%	2	4	2.4
	Range	41-96%	1-4	3-4	1-4
adverse n=5	Median	38%	2	3.7	1
	Range	31-82%	1.3-4	3.3-4	1-4

Table 3.3

We will report about subcategory 1 of the MOS, *fidgety movements,* in subchapter 3.3.2. Comparing subcategories 2 to 4 across the three groups, we did not find any significant difference (Kruskal Wallis Test, p-values between 0.11 and 0.77; **Table 3.3**). But, if we merged *normal* and *mild* and compared them to *adverse,* the posture was less optimal in the *adverse* (Mann-Whitney-U Test, $p<0.05$).



The medians of the MOS scores (expressed in %) for *normal*, *mild* and *adverse* groups for each age period.

Fig. 3.1

Subcategory 5 refers to the *overall quality of motor repertoire.* As none of the infants scored cramped-synchronized the variable became dichotomous: normal, smooth and fluent vs. jerky, monotonous, tremulous (Fisher's Exact Test, p=0.51; **Table 3.4**)

	Subcategory 5	
Groups	**predominantly normal** (smooth and fluent)	**predominantly abnormal** (jerky, monotonous, tremulous or stiff)
normal	2	4
mild	2	6
adverse	-	5

Table 3.4

3.3.2 *Fidgety Movements*

As mentioned in subchapter 3.2.3 the assessment of fidgety movements is subcategory 1 of the MOS. Being aware of the predictive power of fidgety movements for the neurological outcome of infants with brain lesions[124], we specifically focused on this movement pattern.
As can be seen in Fig. 3.2, all but one of the infants with a later adverse outcome were scored as absent fidgety movements. Only Case 4 had fidgety movements at 12 weeks; later video-recordings did not allow for the assessment of spontaneous motility. Among the *adverse group*, Case 4 has the less severe outcome namely a mild right upper extremity hemiparesis. Focusing on the infants with a neonatal stroke belonging to the *mild group*, six infants had normal fidgety movements whereas two (Cases 8 and 14) had no fidgety movements. All but one of the normal infants had normal fidgety movements. Only Case 20 who was assessed at 16 weeks (T4) did not show fidgety movements. Comparing the three groups did not result in a significant difference (Fisher's Exact Test, $p=0.12$). However, infants from the *adverse group* had significantly more often no fidgety movements compared to both *normal* and *mild* (Fisher's Exact Test, $p<0.05$; **Table 3.5**).

	FMs		
	present	absent	Total
normal	5	1	6
mild	6	2	8
adverse	1	4	5
Total	12	7	19

Key: FMs (fidgety movements)

Table 3.5

We want to point out that Cases 13 and 19 might have a late onset of fidgety movements as their fidgety trajectory was changing from absent to present only at T3 (13 to 14 weeks; **Fig. 3.2**).

Infant	Age Groups						Outcome
	T1	T2	T3	T4	T5	T6	
1		•					CP - R spastic hemiplegia
2	•					•	CP - R spastic hemiplegia
3	•	•			•		CP - R spastic hemiplegia
4		⊙					Mild R UE hemiparesis
5						•	Myotonic Distrophy
6		⊙	⊙		⊙	⊙	Average Bayley-III at 18 months
7				⊙			Average Bayley-III at 18 months
8	•	•	•	•	•		Average Bayley-III at 11 months
9		⊙			⊙	⊙	Average Bayley-III at 8 months
10	⊙	⊙	⊙	⊙		⊙	TD assumed
11			⊙	⊙			TD assumed
13	•	•	⊙	⊙		⊙	TD assumed
14			•				TD assumed
17	⊙	⊙		⊙			Typically Developing
18		⊙	⊙		⊙	⊙	Typically Developing
19		•	⊙	⊙	⊙		Typically Developing
20				•			Typically Developing
21	⊙	⊙	⊙	⊙	⊙	⊙	Typically Developing
22		⊙	⊙	⊙	⊙	⊙	Typically Developing

Key: CP (cerebral palsy); R (right); UE (upper extremity); TD (typical development);
⊙ *fidgety movements* present; • *fidgety movements* absent.

Fig 3.2

3.3.3 *The Assessment of Segmental Movements: isolated wrist and finger movements*

All but one infant with a left-sided or left-dominant lesions who developed a right-sided hemiplegia had more wrist movements on the ipsilesional-side (**Table 3.6**). Only Case 4 with the mild right upper extremity hemiparesis had an equal number of wrist movements. All other infants with stroke who did not develop CP and all control infants had the same amount of movements in both wrists (**Table 3.6**).

Infant	Side	Side preference of segmental wrist movements across ages	Outcome
1	L	+L	CP - R spastic hemiplegia
2	L	+L	CP - R spastic hemiplegia
3	L>R	+L	CP - R spastic hemiplegia
4	L>R	L=R	Mild R UE hemiparesis
6	L=R	L=R	Average Bayley-III at 18 months
7	R>L	L=R	Average Bayley-III at 18 months
8	L=R	L=R	Average Bayley-III at 11 months
9	R	L=R	Average Bayley-III at 8 months
10	R	L=R	TD assumed
11	L	L=R	TD assumed
12	L=R	L=R	TD assumed
13	L=R	L=R	TD assumed
14	L=R	L=R	TD assumed
17	control	L=R	Typically Developing
18	control	L=R	Typically Developing
19	control	L=R	Typically Developing
20	control	L=R	Typically Developing
21	control	L=R	Typically Developing
22	control	L=R	Typically Developing

Key: L (left); R (right); +L (more segmental movements on the left side); +R (more segmental movements on the right side); CP (cerebral palsy); UE (upper extremity); TD (typical development).

Table 3.6

Infant	Side	Side preference of insolated finger movements across ages	Outcome
1	L	L=R	CP - R spastic hemiplegia
2	L	+L	CP - R spastic hemiplegia
3	L>R	+L	CP - R spastic hemiplegia
4	L>R	*fisting*	Mild R UE hemiparesis
6	L=R	+R	Average Bayley-III at 18 months
7	R>L	L=R	Average Bayley-III at 18 months
8	L=R	L=R	Average Bayley-III at 11 months
9	R	L=R	Average Bayley-III at 8 months
10	R	L=R	TD assumed
11	L	L=R	TD assumed
12	L=R	+R	TD assumed
13	L=R	L=R	TD assumed
14	L=R	+R	TD assumed
17	control	L=R	Typically Developing
18	control	L=R	Typically Developing
19	control	+R	Typically Developing
20	control	L=R	Typically Developing
21	control	L=R	Typically Developing
22	control	L=R	Typically Developing

Key: L (left); R (right); +L (more segmental movements on the left side); +R (more segmental movements on the right side); CP (cerebral palsy); UE (upper extremity); TD (typical development).

Table 3.7

For the isolated finger movements the results were not that clear. Only Cases 2 and 3 showed a predominance of left-sided finger movements corresponding to the side of the lesion and the outcome. Three infants of the mild group and one normal infant exhibited more finger movements on the right side. Those infants had a bilateral lesion. All remaining infants had no difference concerning the isolated finger movements irrespective of the medical history or outcome (**Table 3.7**). Due to his outcome, we did not include Case 5 in Tables 3.6 and 3.7.

3.3.4 *The Assessment of Additional Asymmetries*

In addition to wrist and finger movements, which have been previously discussed as early markers of unilateral CP[169, 172] we also focused on opening and closing of the hand, kicking, trunk bending, foot-foot contact and head position. None of these movement patterns showed a side preference which was related to stroke and/or outcome.

3.3.5 *Early behavioural markers for unilateral CP*

In our sample of 13 infants with neonatal stroke, only four infants (31%) developed a unilateral CP (Cases 1 to 4). **Table 3.8** summarizes the findings of our assessment during early infancy. None of the infants obtained 50% of the maximal MOS.

Cases	Overall MOS(%)	Overall MotRep (*predominant*)	FMs	wrist	finger
1	43%	monotonous	●	+L	L=R
2	38%	stiff	●	+L	+L
3	31%	monotonous	●	+L	+L
4	35%	jerky	⊙	L=R	*fisting*

Key: MOS (Motor Optimality Score); MotRep (Motor Repertoire, subcategory 5); L (left); R (right); +L (more segmental movements on the left side); FMs (fidgety movements); ⊙ *fidgety movements* present; • *fidgety movements* absent.

Table 3.8

None of those infants had a smooth and fluent overall movement character. With the exception of Case 4 (outcome: mild right upper extremity hemiparesis), fidgety movements were absent and an asymmetry of segmental movements, especially wrist movements, marked a high-risk for a unilateral CP (**Table 3.8**).

3.4 Discussion

Our meticulous observation of age-adequate movement and postural patterns adds to the understanding of early behaviours in infants with neonatal stroke who eventually will develop neurological impairment and those who will rather follow a typical development. In the following sub-chapters we will discuss our results in the same sequence as we presented them:

3.4.1 *The Assessment of the Motor Repertoire*

Due to organisational reasons but also not optimal recording conditions we had a number of missing data: not each infant was recorded in each age period and not all available recordings were assessable for spontaneous behaviours. Instead of a more preferable individual trajectory we therefore had to calculate an "overall MOS across ages" indicating a percentage score related to the maximum score obtainable per infant. Comparing these percentage scores we could easily notice that the *normal* and *mild group* (84% and 70% respectively, **Table 3.3**) scored more optimal than the *adverse group* (38%, **Table 3.3**); or, in other words, the % overall MOS across ages was significantly related to the neurodevelopmental outcome.

To the best of our knowledge the MOS has been never applied in infants with neonatal stroke but it has been frequently applied in high-risk preterm infants. Bruggink et al.[187] showed that a reduced MOS between 11 and 16 weeks post-term age correlated with a higher risk for a preterm infant to develop complex minor neurologic dysfunction (MND) or CP. Butcher et al.[188] added that a reduced MOS was significantly associated to later cognitive impairments. Yang et al.[189] found that the MOS was related with the level of functional mobility in both children born at term and preterm: a higher MOS meant a better level on the GMFCS (Gross Motor Function Classification System). Yang et al. also found that the majority of the participants who developed CP, not only had a lack of fidgety movements but

also other abnormal patterns including an abnormal (often cramped-synchronized) *overall quality of motor repertoire*. Our finding that Case 4 who developed a mild form of CP (**Table 3.1**) had the less reduced MOS among the *adverse* group is in line with the findings of Yang et al.[189] and Bruggink et al.[190], both studies demonstrated a significant correlation between the degree of the reduction in MOS and the severity of CP later on.

The MOS is a composite score obtained by the sum of five different subcategories: *fidgety movements*, *age-adequacy of the motor repertoire*, *quality of movement patterns*, *observed postural pattern* and *overall quality of motor repertoire*. Due to the clinical relevance of fidgety movements we will discuss these movements separately (3.4.2). Comparing *age adequacy of the motor repertoire* and *quality of the movement patterns* across the three groups we could not find any difference. The same held true for the *overall quality of motor repertoire*. As already mentioned in the methodology (**3.2**), some of our infants participated in a previous study by Chen et al.[183]: in this study they investigated midline toy exploration and fine and gross motor skills between 2 and 7 months of age in infants at risk for hemiplegic CP. Infants with neonatal stroke differed from infants with typical development because of poor performance in midline behaviours and fine and gross motor scores on the Bayley Scales of Infant Development III. Our results did not confirm their findings, but we focused on the assessment of spontaneous motility towards the midline (e.g. hand-hand contact, foot-foot contact), not induced by manipulation of toys.

Although none of the infants with neonatal stroke and CP showed a normal, smooth and fluent movement character, two infants from the *mild* and other two infants form the *normal group* also presented an abnormal movement character, i.e. predominantly monotonous, jerky, stiff or tremulous. Only for the *observed postural patterns* we found that the posture was less optimal in the *adverse group* than in the *mild* or *normal* groups. This indicates once more that it is the fidgety movements being the most eminent pattern leading to the differences in the MOS between the groups. Also Bruggink et al.[190] discussed that it is mainly the presence/absence of fidgety movements contributing to the prediction of the neurological outcome whereas the concurrent movements might be less relevant.

Yuge et al.[184] found that those 23 infants who developed normally showed a heterogeneous quality of *movement* and *postural patterns*: while fidgety movements were present in the majority of them (87%), the quality of movement patterns and postures was only optimal in 8 infants (35%). Also according to the study by Bruggink et al.[187], nearly half of the infants with an abnormal *overall quality of motor repertoire*, i.e. monotonous or jerky, at the age of 2 to 5 months were later classified as normal. However, recently Fjørtoft et al.[175] and

Grunewaldt et al.[191] reported that preterm born children with monotonous, jerky and/or stiff movements at 3 to 5 months were more likely to have cognitive impairments at age 10 compared to preterm born children with a smooth and fluent movement character during early infancy.

3.4.2 *Fidgety Movements*

Previous studies have demonstrated the predictive power of fidgety movements for the neurological outcome of infants with brain lesions[124, 169, 184].

In our small sample we found that all but one of the infants of the *adverse group* were scored as absent fidgety movements at each age-session. The only infant belonging to this group and presenting fidgety movements is the one with the less severe neurological outcome (Case 4 with mild right upper extremity hemiparesis); from him we, unfortunately, have only one video-recording assessable at 12 weeks post-term age. In this video his MOS was 23 out of 28- which is reduced but better than the MOS of his peers in the *adverse* group. The relatively high MOS was due to the fact that he showed clear *fidgety movements* although his *observed postural patterns* and *overall quality of motor repertoire* were very poor. In the study by Yang[189] only one of the 79 children with CP had normal fidgety movements, and this boy, born full-term, developed a mild unilateral spastic CP as well.

Already in 1997, Prechtl et al.[124] emphasised the importance of fidgety movements because it allows valid prediction about later neurological outcome to be made long before the first signs of spasticity appear. In this study they collected data on the normality, abnormality or total absence of fidgety movements of 130 infant classified as "low risk" or "high risk" on the basis of ultrasound scans. The authors found that 67 of 70 infants (96%) with normal fidgety movements had a normal long-term neurological outcome but three of them had an abnormal outcome: one had motor retardation while two developed a very mild form of CP (one minimal monoplegia of a leg and the other a mildest form of hemiplegia). This did not reduce the predictive power of fidgety but could strengthen the eventuality to find fidgety movements in infants with an adverse but "mild" neurological outcome[124].

By contrast, the majority of infants from *normal* and *mild* groups (83% and 75% respectively) had normal fidgety movements, confirming that the presence of fidgety movements is as an excellent marker for a normal neurological outcome.

3.4.3 *Assessment of Asymmetries*

One of the aims of this study was to confirm the previously reported significant correlation between an asymmetry of segmental movements and the presence of later hemiplegia in infants with neonatal stroke. Previous studies have demonstrated that, contralateral to the side of the lesion, the so-called "segmental movements" (i.e., distinct movements of hand and feet, fingers and toes, occurring either isolated or as a part of GMs) were reduced or even absent[142, 169].

We therefore focused explicitly on segmental movements of the wrist, defined as movements of moderate speed at the level of the wrist joint, including rotations, palmar flexion an extension, and ulnar or radial flection and on the independent digit movements, including all of the digit movements such as isolated movement of one finger, simultaneous movement of two or more fingers and sequential movement of two or more fingers[172]. Our results showed that in infants with later right spastic hemiplegia segmental movements were clearly asymmetrically: all three infants had a preference of wrist movements on the left side (ipsilesional). The only infant belonging to the *adverse group* who did not show a side-prevalence was again the infant with the less severe outcome (Case 4 with mild right upper extremity hemiparesis). All other infants with stroke who later developed normally did not show a side-preference in segmental movements, suggesting that their brain injury did not become functional already at an early age. All infants from the control group had an equal distribution of segmental wrist movements. The results confirm the previous ones by Guzzetta et al.[172] who reported a significant correlation between asymmetry of wrist movements at 3 months after birth and the presence of later hemiplegia in infants with neonatal stroke. They used a single time point for the assessment, basing their choice on the knowledge of the predictive value of the assessment of GMs performed at 3 months after birth in similar cohorts and on the fact that this time is characterized by important developmental changes. In our study we assessed asymmetries from 9 to 20 weeks and we noticed that the side preference was constant across ages.

Less obvious was the correlation between the asymmetry of isolated finger movements and the neurological outcome. In the *adverse group*, only two infants demonstrated a clear left-sided prevalence, while one of them had no difference concerning the isolated finger movements. In the *mild group* three infants had a right-sided prevalence but this evidence was not in contrast with their medical history because they had bilateral stroke. Also one infant in the *normal group*

showed a right-sided prevalence. Cioni et al.[142] reported that such an asymmetry, though very rarely, could also be observed in infants with a normal neurological development.

We also investigated if kicking might be asymmetrical in infants with a later diagnosis of hemiplegia. But, similar than van der Heide et al. [192], we also did not find any significant difference between the three groups of infants suggesting that kicking might not be affected in case of ipsilateral lesion. Van der Heide and colleagues[192] did a kinematic analysis of kicking at 1 and 3 months post-term age which showed no clear differences between full-term infants without brain injury, low-risk preterm infants without brain injury and preterm infants with severe brain lesions. As we have only a small sample of infants with neonatal stroke and CP, we cannot consider our results as conclusive. However, our findings suggest that infants with neonatal stroke, who later develop hemiplegia, show the same amount of kicking movements in both legs, without any correlation with the side of their brain lesion.

We were also interested in evaluating the eventuality of evident side-preferences in closing or opening of the hand, trunk bending, foot-foot contact and head position, but asymmetries were occasional and sporadic and not related to the side of the lesion or the outcome.

3.4.6 *Early behavioural markers for unilateral CP*

The great advantage of early detecting an increased risk of CP consists of the possibility of intervention long before the emergence of obvious pathological features[168].

By assessing the motor repertoire, especially focusing on fidgety movements and assessing asymmetries in segmental movements between 3 and 5 months post-term age, we have been able to identify those infants who developed normally and those who did not. This is in line with previous studies[142, 168, 174, 193], rejecting the hypothesis of a *silent period* that would prevent an early identification of unilateral CP. The assessment of the motor repertoire, which combines the global visual Gestalt perception with a more detailed analysis of movements and postures, could provide early markers that are associated with future development of CP. The absence of fidgety movements confirmed its predictive power in early detecting infants with high risk to develop CP[168]. In addition to that, to be able to early detect some asymmetries in segmental movements of wrist and fingers could also provide information about location and severity of CP, which can support the traditional neurological examination and neuroimaging techniques that are still essential.

3.4.7 *Limitations of our study*

Neonatal stroke is a rare disease and is often diagnosed after the first months of life, when the signs of motor impairment became obvious[53]. Therefore early and close follow-up studies on a large sample are difficult to conduct. Hence, the major limitation of this study is the small number of patients assessed. In addition, not all infants are recorded or assessable at all time-epochs. Furthermore, we had to use a footage recorded for a different purpose (Chen et al.[183]) hence, sequences with spontaneous movements of the non-manipulated infant were short and hardly exceeding 60s. In addition, the proportion of the participants with neonatal stroke and unilateral CP (18%) is rather small leading to very small sub-groups within our already small sample. We, therefore, are far from drawing general conclusions.

3.5 Final Remarks

The observation of early behaviours certainly adds to the neurofunctional assessment of an infant, especially in infants with brain injury. There is more and more evidence - although in small samples - that an absence of the age-specific fidgety movements, a less optimal movement repertoire at 3 to 5 months after term, and asymmetries in the wrist movements could contribute to the identification of infants with brain injury, such as neonatal stroke, who will develop functional impairments. Early identification of those infants who are at high risk to develop CP enables us to intervene before the clear clinical signs appear. Even though there is actually no proof that early intervention could prevent CP, it may have a positive effect on the quality of spontaneous movements and hence, the child's functional abilities in the future[119, 133, 174].

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ACKNOWLEDGEMENTS 80

ACKNOWLEDGEMENTS

I want to thank Prof. Cioni for his support in this thesis project, his help has been precious in the application process for the grant provided by the University of Pisa, which gave me the possibility to spend three months at the iDN (interdisciplinary Developmental Neuroscience) of Graz for my research. I shall also thank Dr. Guzzetta, who first introduced me in the GMs field and who gave me the material to start my research, providing me at the same time with valuable advices during my work abroad. Thanks to them I could also attend to the basic training GMs course in Modena, which has been determining in improving my knowledge about the Prechtl's Method.

My deepest gratitude goes to Prof. Christa Einspieler and all the other components of the iDN research unit of the Institute of Physiology of Graz: Peter, Dajie, Robert, Magdalena, Iris, Florian, Sahar, Gunter and Hector. I want to thank them for their warm hospitality and kindness. It was an honour to be part of their team, even just for a short period. My work contains a part of each of them and I'm proud of it. I will keep a nice memory of our lunches all together around the *wooden table*. Graz is really nice and, even if it is too rainy and cold for an Italian, they have contributed to make it really comfortable and pleasant.