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Computer-based assessment of general movements

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Doctoral Thesis

NTNU
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Thesis for the degree of
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Tidlig prediksjon av cerebral parese hos spedbarn

Databasert undersøkelse av spedbarnets spontane bevegelsesmønstre

Cerebral parese (CP) er en alvorlig funksjonshemning som kan oppstå som følge av for tidlig fødsel eller andre alvorlige sykdommer i nyfødtperioden. Til tross for betydelige forbedringer innen nyfødtmedisin med redusert dødelighet, har forekomsten av CP ikke gått ned. Mange undersøkelsesmetoder som brukes for å predikere senere funksjonshemning har begrensninger på grunn av høye kostnader, behov for spisskompetanse og lav nøyaktighet. Diagnostisering av CP er vanskelig og tidlig identifisering av barn med CP er viktig for at riktig behandling kan startes mens hjernens plastisitet ennå er stor. Det er derfor behov for nøyaktige undersøkelsesverktøy for tidlig avklaring om mulig utvikling av CP.

Undersøkelse av spedbarnets spontane bevegelser med metoden General movement assessment (GMA) har vist seg å være en god metode for undersøkelse av sentralnervesystemets funksjon. Spesielt har fravær av såkalte fidgetybevegelser (små, sirkulære og rytmiske bevegelser i hele kroppen) ved 2-5 måneders alder vist seg å være en viktig markør for senere CP utvikling. Undersøkelse av slike bevegelser baseres på observasjon av barnets spontane bevegelser i en videofilm og kan bare utføres av fagfolk med høy spisskompetanse og mye erfaring. Det har derfor vist seg at GMA metoden er lite tilgjengelig og i liten grad benyttes ved oppfølging av barn som er i risiko for CP. Databasert videoanalyse av spontanbevegelser har de senere årene blitt mer tilgjengelig på grunn av betydelig teknologisk utvikling.

Formålet med denne avhandlingen var å undersøke GMA metodens evne til å predikere CP under norske forhold, samt å evaluere enigheten mellom to observatører som klassifiserer fidgetybevegelser. Det var videre et mål å gjøre ekspertkunnskap om fidgetybevegelsers karakteristika til noe objektivt målbart. Basert på identifiserte målbare bevegelseskarakteristika var det videre et mål å utvikle en databasert metode for å kunne gjenkjenne fravær av fidgetybevegelser i en videofilm og til slutt å teste denne metodens evne til å predikere CP.

Studien som undersøkte GMA metodens evne til å predikere CP bekreftet tidligere studiers resultater om god nøyaktighet også brukt under norske forhold. Studien bekreftet videre høy enighet mellom to observatører i klassifiseringen av fidgetybevegelser. Basert på kunnskapen fra en ekspert viste det seg mulig å fremstille bevegelseskarakteristika hos barn med og uten

fidgetybevegelser grafisk. Dette ga konkrete ideer til utvikling av målbare egenskaper i bevegelsesmønstrene. Den tredje studien dokumenterte en nøyaktig, databasert videoanalyse for gjenkjenning av objektive karakteristika ved fravær av fidgetybevegelser. En prognostisk datamodell basert på bevegelseskarakteristika hentet fra videobildet viste i siste studie svært god evne til å forutsi CP ved fem års alder. Den data baserte metoden viste i tillegg en svært god evne til å forutsi gående eller ikke gående funksjon hos en liten gruppe barn med CP.

Denne avhandlingen bidrar med ny kunnskap om en ny metode for databasert videoanalyse og tidlig prediksjon av CP. Metoden som tar i bruk objektiv analyse av spedbarns bevegelser filmet med et vanlig videokamera kan i nær fremtid få stor betydning for tidlig diagnostisering av CP. Fremtidig forskning kan ved hjelp av denne nye metoden sannsynligvis bringe nytt lys over effekten av ulike treningstiltak gitt til barn med CP.

Kandidat: Lars Adde
Institutt: Institutt for laboratoriemedisin, barne- og kvinnesykdommer
Veiledere: Ragnhild Støen, Jorunn L. Helbostad, Øyvind Stavdahl

Ovennevnte avhandling er funnet verdig til å forsvares offentlig for graden ph.d i klinisk medisin.
Disputas finner sted i Øya Helsehus, auditoriet ØHA11, St. Olavs Hospital og NTNU, Trondheim
Onsdag 28. april 2010 klokken 12.15

To my children,

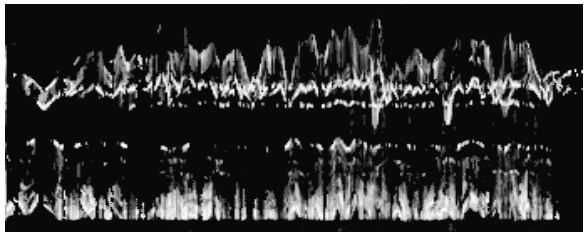
who have inspired me to try to understand more about movement and life.

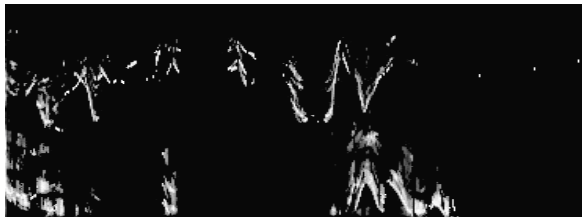
Il moto é causa d'ogni vita.

LEONARDO DA VINCI

Movement is the cause of all life.

TRONDHEIM 2010





The art of motiongrams displaying normal and abnormal infant spontaneous movements

"Prognostic models are not meant to take over the job of the doctor. They are intended to help doctors make decisions by providing more objective estimates of probability as a supplement to other relevant clinical information and test results. Furthermore, they improve understanding of the determinants of the course and outcome of patients with a particular disease"

(Moons et al. 2009)

Contents

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List of papers

This thesis is based on the following papers:

Paper I
General movement assessment: Predicting cerebral palsy in clinical practise
Lars Adde, Marite Rygg, Kristin Lossius, Gunn Kristin Øberg, Ragnhild Støen
Early Human Development
2007; 83:13-8

Paper II
ENIGMA-Enhanced interactive general movement assessment
Pål Berge, Lars Adde, Gabriela Espinosa, Øyvind Stavdahl
Expert Systems with Applications
2008; 34: 2664-72

Paper III
Using computer-based video analysis in the study of fidgety movements
Lars Adde, Jorunn L. Helbostad, Alexander Refsum Jensenius, Gunnar Taraldsen, Ragnhild Støen
Early Human Development
2009; 85: 541-7

Paper IV
Early prediction of cerebral palsy by computer-based video analysis of general movements: a feasibility study.
Lars Adde, Jorunn L. Helbostad, Alexander R. Jensenius, Gunnar Taraldsen, Kristine H. Grünewaldt, Ragnhild Støen
Developmental Medicine & Child Neurology
2010; Feb 24 (Epub ahead of print)

Abbreviations

BW	birth weight
CNS	central nervous system
CP	cerebral palsy
ELBW	extremely low birth weight
ENIGMA	Enhanced interactive general movement assessment
FM	fidgety movements
GMA	General movement assessment
GM	general movements
GMFCS	Gross motor function classification system
GMT	General Movement Toolbox
GA	gestational age
VLBW	very low birth weight

Neonate: *Neonatus* (Latin) = refers to an infant in the first 28 days of life (less than a month old)

Summary

Cerebral palsy (CP) is the most serious chronic motor disability that can occur in infants. Despite improvements in care and reduced mortality among high risk term and preterm infants, the prevalence of CP is stable. Diagnosing CP is difficult and early identification of CP might be beneficial for early treatment when the plasticity of the brain is high. Hence, there is a need for accurate assessment methods to provide early clarification about CP development.

Assessment of general movements (GMs), a part of the spontaneous movement repertoire, has proven to be reliable and sensitive in the early assessments of infants to identify CP. Using video recordings of infant spontaneous motor activity, observers classify the qualities of general movements into categories. In particular, the absence of so-called fidgety movements in infants at 9-20 weeks post-term age has been shown to be a strong marker for later CP. However, the GM assessment is qualitative and highly dependent on skilled personnel. It is reported to be limited in use in ordinary clinical practice. Recently, computer-vision-based human motion analyses have become possible, providing an inexpensive, non-obtrusive solution for the analysis of movement using video recordings.

The aim of this thesis, which constitutes four different scientific studies, was fourfold; 1) to verify the GM assessment for prediction of CP used in a clinical setting and evaluate the inter-rater reliability in the assessment of fidgety movements, 2) to elicit expert knowledge about fidgety movements and identify possible objective characteristics using visual displays, 3) to develop a computer-vision-based method for identification of infants with present and absent fidgety movement characteristics, and 4) to evaluate the accuracy of the developed computer-vision-based method in the prediction of later CP.

The results showed that GM assessment by the use of qualitative assessment of fidgety movements demonstrated high sensitivity and specificity in the early prediction of CP. The inter-rater reliability in the assessment of fidgety movements was good. The use of visual displays for observation of absent or present fidgety movements revealed important expert knowledge about periodic movement patterns. The use of a computer-vision-based tool, the General Movement Toolbox, demonstrated ability to detect absent and present fidgety movement characteristics and high sensitivity and specificity for prediction of CP during the

fidgety movement period. The General Movement Toolbox also demonstrated high sensitivity and specificity, correctly predicting ambulatory or non-ambulatory function for 9 of 10 children with CP.

This thesis provides a novel computer-based method for early prediction of CP in young infants based on a single video recording. The assessment instrument General Movement Toolbox is presented, showing promising prediction of CP and ambulatory versus non-ambulatory function in children with CP. This thesis adds an early objective detection of movement hallmarks for later neurological disease to the field of neuromotor assessment of infants. It brings hope for earlier and more precise prediction of CP and evaluation on early intervention strategies in future research.

CHAPTER 1: Introduction

The first baby incubator was introduced by Dr. Tarnier in France in 1880, and a pavilion for weakling newborns, equipped with 12 incubators was opened in Paris in 1893 – a milestone in neonatal care (Toubas and Nelson, 2002). Dr. Budin extended the care of the discharged infants, and stepdown units called *pouponniers* were created to assure the transition of the infants to the home. As a consequence, infant mortality decreased rapidly (Toubas and Nelson, 2002). After the Second World War, special care baby units (SCBUs) were established in many hospitals and by the early 1980s paediatricians could train and qualify in the sub-speciality of neonatal medicine. Today, neonatal intensive care units (NICUs) concentrate on treating very small, premature, or otherwise sick newborns. NICUs have greatly increased the survival of premature and sick infants (Larroque et al., 2008), and between 1980 and 2004 neonatal mortality rates in the United States declined by almost 50% (Kliegman et al., 2007). Before the NICUs, infants of birth weight less than 1400 grams (about 30 weeks' gestation) rarely survived. Today, infants with a birth weight above 500 grams or a gestational age above 25 weeks have a fair chance of survival. However, many challenges are faced by small or immature newborns, and this has led to concern about the long-term outlook for saved neonates.

The World Health Organization refers to preterm birth as birth of a baby of less than 37 weeks gestational age (Kliegman et al., 2007). The untimely birth exposes the newborn to an environment for which it is not ready, and may cause major problems with respiration, circulation, nutrition and thermoregulation. Morbidity and mortality are inversely correlated to gestational age, and the most immature infants, born before 28 weeks of gestation or with a birth weight below 1000g (Extremely Low Birth Weight or ELBW infants) are in general especially susceptible to long-term disability. These include severe cognitive and neurologic conditions, such as cerebral palsy (CP), mental retardation, deafness, and blindness, as well as milder problems such as learning disabilities and attention-deficit hyperactivity disorder (Lorenz et al., 1998, Marlow et al., 2005). The presence of intra-uterine growth retardation, intracranial haemorrhage (ICH) and periventricular leukomalacia (PVL) in ELBW babies will further increase the risk of adverse neurodevelopmental outcome (Vollmer et al., 2003, Roze et al., 2009). In term newborns, perinatal asphyxia and hypoxic ischaemic encephalopathy (HIE) are a major cause of neurologic disability (Dilenge et al., 2001).

Cerebral palsy is the most serious chronic motor disability that may occur in these high-risk infants. Despite improvements in care and reduced mortality among extremely premature infants, the prevalence of CP is stable (Clark and Hankins, 2003). Early diagnosis of CP is complex and difficult; a diagnosis of CP might not be obvious before the age of 2 years and the sub-type not before the age of 4 years (Hadders-Algra, 2004). Early identification of CP might be beneficial for early treatment when the plasticity of the brain is high and may lead to more accurate follow-up of children and families most in need. Hence, there is a need for accurate assessment techniques to provide early clarification about possible CP development.

The infant brain is in a continuous process of remodelling, and development consists of the creation of new elements as well as elimination of elements (Hadders-Algra, 2004). Developmental outcome is heterogeneous and may be associated with risk factors, such as gestational age, birth weight, brain damage acquired in the pre- or perinatal period or subsequent illnesses. Typically, neurological dysfunctions in young infants are expressed by means of generalized and non-specific dysfunctions. The brain changes can also induce a disappearance of observable dysfunctions present at an early age (Hadders-Algra, 2004).

There is a diversity of techniques available to assess the brain function at an early age. Various forms of assessment techniques require no equipment and can be performed bedside. More sophisticated technical assessments are cerebral ultrasound (CUL), magnetic resonance imaging (MRI) and computer tomography (CT). Neuro-physiological tests such as electroencephalogram recordings as well as visual and somatosensory evoked potentials are also used. Common to all these assessment techniques is that they are resource intensive and require highly skilled personnel to perform and interpret them, limiting their availability. It has been suggested that parents of children with developmental disorders are concerned significantly later than physicians are about the developmental status of their children (Ehrmann Feldmann et al., 2005). Altogether, this emphasizes the important role of the paediatrician and the physiotherapist in the assessment of neuromotor function in young infants.

A new technique for neuromotor assessment in young infants has been developed during the past two decades. The approach involves functional assessment of the young nervous system and has principally been presented by Prechtl and Hadders-Algra and co-workers (Einspieler and Prechtl, 2005, Prechtl et al., 1997, Einspieler et al., 1997, Hadders-Algra, 2004).

Assessment of general movements (GMs), a part of the spontaneous movement repertoire, has shown to be reliable and sensitive in the early assessments of infants to identify neurological deviations which may lead to CP (Valentin et al., 2005, Fjortoft et al., 2009, Einspieler et al., 2004, Hadders-Algra, 2004). Using video recordings of infant spontaneous motor activity, observers classify the qualities of general movements into categories. In particular, the absence of so-called fidgety movements (FMs) in infants at 9-20 weeks post-term age has been shown to be a strong marker for later disability and CP in particular (Prechtl et al., 1997, Adde et al., 2007, Seme-Ciglenecki, 2003, Hadders-Algra, 2004, Einspieler et al., 2004). General movement assessment (GM assessment) has been introduced with the potential fore accurate prediction of later CP development at a much earlier age than was previously possible, and it is a non-intrusive, easily learned, and cost-effective method (Einspieler et al., 2004, Hadders-Algra, 2004).

Despite the documentation of high accuracy in predicting CP, questions have been raised about the GM assessment technique. Although some documentation on GM assessment is from outside the expert group from which it originated, there is still a major portion published by the same group of researchers. The technique is qualitative, highly dependent on skilled personnel, and requires education and updating to be performed. For clinicians working alone, lacking the important possibility to discuss difficult cases with experienced colleagues, judgement of movement qualities according to GM assessment might be difficult to trust (Adde et al., 2007). Hence, the implementation, generalizability and overall utility of the GM assessment technique in clinical use have been questioned (Adde et al., 2007, Palmer, 2002, Palmer, 2004). It is reported that GM assessment is limited in use in ordinary clinical practice (Garcia et al., 2004).

New motion capture technologies have made it possible to perform quantitative analyses of movement and, thereby, discrimination of normal versus pathological movement based on objective criteria. However, such methods are often restricted to laboratories because of the need for comprehensive instrumentation and advanced analyses. Recently, computer-vision-based human motion analyses without markers have provided an inexpensive, non-obtrusive solution for the estimation of body postures using video recordings (Poppe, 2007). In addition to extracting quantitative measures from the movements in the video recording, such solutions might also visualize the qualities of movement.

Today, it is acknowledged that young infants at high risk need follow-up for the possible detection of CP after discharge from hospital. Follow-up programmes have been implemented in most tertiary care centres caring for these infants and provide specific intervention programmes and accurate information to parents about their infant's capabilities and prognosis. In most cases, the follow-up programmes use a multidisciplinary approach were the paediatric physiotherapist plays an important part. In-depth knowledge about normal motor development, subtle symptoms of delayed motor development and parental counselling gives the physiotherapist a unique possibility to detect motor problems associated with later CP and to give adequate and specific advice. With early assistance provided by an objective computer-based movement assessment tool, decision making with respect to possible CP development and further intervention strategies and follow-up might be improved.

The overall purpose of the investigation presented in this thesis was to verify the predictive value of absent and present fidgety movements used in ordinary clinical practice, to develop a new computer-based prognostic model for detection of infants with or without fidgety movements, and finally to test the ability of this early computer-based prognostic model to predict CP in high-risk young infants. The background for this work will be presented in the next section.

CHAPTER 2: Background

Cerebral palsy

Cerebral palsy (CP) is a common and serious chronic motor disability, beginning in early childhood and persisting through the lifespan (Rosenbaum et al., 2007). It is generally accepted that the risk of CP increases with decreasing gestational age of live-born infants (Joseph et al., 2003) and as a diagnostic term, CP is used to describe a group of motor syndromes resulting from disorders of early brain development. Historically, it has been considered a static condition, but later it has been recognized that the neurologic and clinical features of CP often change or progress over time (Kliegman et al., 2007). In 2004, an International Workshop on Definition and Classification of Cerebral Palsy underlined that CP is not an etiologic diagnosis, but a clinical descriptive term. It was expressed that persons with neurodevelopmental disabilities often present impairments of a wide range of functions that may or may not include severe motor manifestations (Rosenbaum et al., 2007). The latest definition and classification of cerebral palsy was stated by the International Workshop participants in a report as follows in April 2006: "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 disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour, by epilepsy, and by secondary musculoskeletal problems" (Rosenbaum et al., 2007).

Diagnosis and classification of cerebral palsy

A CP diagnosis traditionally depends upon a combination of clinical findings including motor delay, neurologic signs, persistence of primitive reflexes, and abnormal postural reactions. Clinical signs evolve as the nervous system matures and a definitive diagnosis usually requires serial examinations. The diagnosis of CP in infants is traditionally assured by 2 years of age, but a reassessment after age 4 years should be provided to acknowledge the changing clinical picture in young children with motor disorders (Cans, 2000). The Surveillance of Cerebral Palsy in Europe (SCPE) has provided a consensus definition of CP, a decision tree for the diagnostic procedure and a classification tree for CP sub-types (Cans, 2000). The decision tree for diagnosis is shown in Figure 1, classification of CP sub-types in Figure 2 and both are used with permission from the Surveillance of Cerebral Palsy in Europe (SCPE) (Cans, 2000).

The SCPE definition of CP includes the following five key elements: CP is a group of disorders, i.e. it is an umbrella term; it is permanent but not unchanging; it involves a disorder of movement and/or posture and of motor function; it is due to a non-progressive interference/lesion/abnormality; this interference/lesion/abnormality is in the developing /immature brain (Cans, 2000). Registration in the Cerebral Palsy Registry of Norway (CPRN) is based upon the definition used in SCPE and is well-established among paediatricians in Norway (Andersen et al., 2008). The translated version for inclusion/exclusion of CP in the Cerebral Palsy Registry of Norway is the procedure used in our studies (appendix 1).

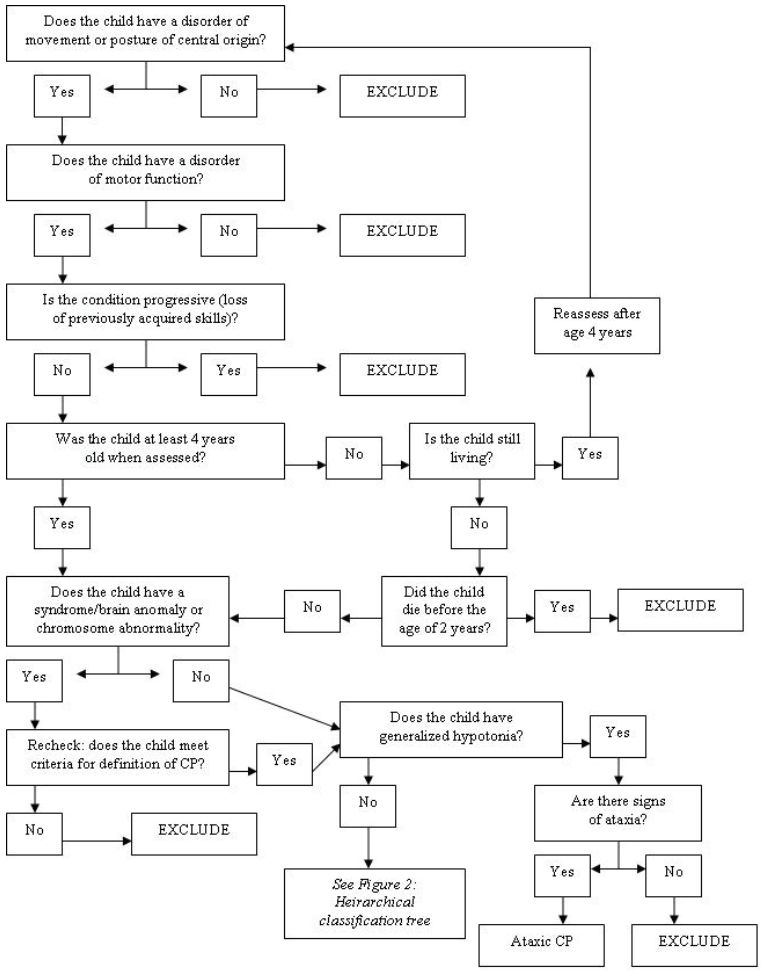

Figure 1: Decision tree for diagnosing cases of cerebral palsy. The figure is adapted with permission from Surveillance of Cerebral Palsy in Europe (SCPE) (Cans, 2000)

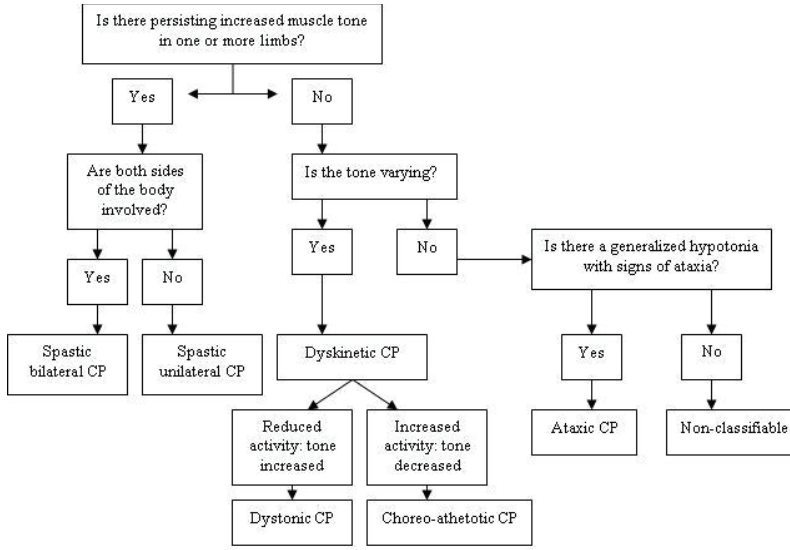

Figure 2: Hierarchical classification tree of CP sub-types. The figure is adapted with permission from Surveillance of Cerebral Palsy in Europe (SCPE) (Cans, 2000)

Cerebral palsy prevalence and risk factors

Prevalence

The global prevalence of CP has remained stable at about 2 to 3 per 1000 for several decades (Clark and Hankins, 2003). Studies of CP prevalence in China, Malta, Slovenia and India all demonstrate CP rates between 1.2 and 2.3 per 1000, identical to, or in some cases lower than, what is seen in developed countries (Kavcic and Perat, 1998, Sciberras and Spencer, 1999, Liu et al., 2000, Razdan et al., 1994). In Sweden, a prevalence of 2.12 per 1000 in the period 1991-94 (Hagberg et al., 2001) and 1.92 per 1000 in the period 1995-98 (Himmelmann et al., 2005) has been reported. The prevalence of CP in Norway has been reported to be similar, with 2.1 per 1000 live births (Andersen et al., 2008). The stable global prevalence confirms CP as primarily a developmental event, not influenced by current obstetric technologies available in developed countries (Clark and Hankins, 2003).

Population analyses of CP often report prevalence in term and preterm infant groups. Prevalence of CP has shown an increase over time among infants with birth weights <2500 g, but no change in the prevalence of CP among infants with birth weights >2500 g (Clark and Hankins, 2003, Himpens et al., 2008). A study from Sweden comprised 170 children with CP

born in 1995-1998. This study reported the CP prevalence to be higher the lower gestation and birth weight (Himmelmann et al., 2005).

Risk factors

Prematurity

Preterm infants have increased risk of CP, accounting for 25% of all patients (Himmelmann et al., 2005, Nelson, 2008). Intrauterine infection or inflammation and prolonged rupture of membranes are important antecedents of preterm birth and CP in prematurely born children. There is a potential chain of causal links for CP development in which the cause of preterm delivery may also be a cause. In addition the prematurity itself and brain injury in the early-born fetus are potential causes. A genetic contribution to preterm birth is estimated to account for 20% to 40% (Nelson, 2008).

Genetic susceptibility

Several studies have been conducted on the impact of genetic factors and CP, and it has been inferred that 40% of cases of CP had a genetic basis (48% of term and 24% of preterm cases) (Keogh and Badawi, 2006).

Perinatal asphyxia and neonatal encephalopathy

For decades, birth asphyxia was believed to be the predominant aetiology of CP. It is now believed that 70-80% of CP cases are due to prenatal factors with 10% to 28% of CP cases due to birth asphyxia in term and near-term infants (Keogh and Badawi, 2006). Birth asphyxia can cause CP, but probably an asphyxia-ischaemia can interact with other causal factors such as inflammation, the occurrence of both further multiplying risk (Nelson, 2008, Nelson and Chang, 2008). In some studies, an Apgar score of 0 to 3 at five minutes has indicated an increased risk of CP (Nelson and Ellenberg, 1981).

Birth asphyxia is a well-known and important contributor to neonatal encephalopathy (e.g. seizures, coma, hypotonia). Infants with moderate to severe intrapartum hypoxia-ischaemia often have encephalopathy and the outcome depends on the severity of the hypoxic-ischaemic encephalopathy (HIE). Infants with severe encephalopathy have an increased risk of later neurologic sequelae (Nelson, 2008). Promising results regarding prevention of CP in term and near-term infants by neuroprotection with hypothermia for neonatal encephalopathy

secondary to presumed acute hypoxic-ischaemia at birth, have been reported (Shankaran, 2008).

Ischaemic stroke and intracranial haemorrhage

Arterial ischaemic stroke has been recognized as a major cause of CP in recent years after the application of computer tomography (CT) and magnetic resonance imaging (MRI) for infants and young children. Lesions are typically identified by cranial imaging studies following a neonatal seizure (Nelson, 2008). Some of these infants display neurologic depression and encephalopathy and erroneously receive a diagnosis of "birth asphyxia" or "hypoxic-ischaemic encephalopathy" (Nelson, 2008).

Intrauterine infection

Infections can be transmitted from mother to infant, affect the brain of the infant, and produce motor disability like CP (Nelson and Grether, 1999). There are now many studies of term and near-term infants with consistent findings on the association of maternal infection or fever with a low Apgar score, neonatal encephalopathy and seizures, and increased CP risk (Nelson, 2008, Nelson and Grether, 1999, Nelson and Chang, 2008). Further, it is suggested that uterine infections play a role in the initiation of preterm labour and contribute to the development of central nervous system injury (Clark et al., 2008).

Motor function in cerebral palsy

In 1997, Palisano and co-workers described the development of a Gross Motor Function Measure (GMFM) to classify gross motor function in children with CP (Palisano et al., 1997). The Gross Motor Function Measure was extended by the construction of gross motor function curves for a 5 level Gross Motor Function Classification System (GMFCS) and this was reported in 2000 (Palisano et al., 2000). The inter-rater reliability, the stability over time of a child's GMFCS level and the validity of the GMFCS in predicting walking in children with CP were reported the same year (Wood and Rosenbaum, 2000).

Interventions to improve motor function

Postural dysfunction in CP may be seen as the reduced capacity to modulate postural activity in specific situations and increased antagonist coactivation (de Graaf-Peters et al., 2007). The motor dysfunction includes delay in movement onset, poor force production, poor timing of force generation, and difficulties with antigravity postural control (Bartlett and Palisano,

2000, Ustad et al., 2009, Mayston, 2001). Children with CP have such specific constraints on movement, resulting in reduced experience and variation in motor activities (Ustad et al., 2009, Mayston, 2001).

Infants with CP have potential for enhanced function. Given that experience is important in shaping the developing nervous system, and that practice and task-specific training are essential in motor learning, physiotherapy should have an effect on motor function and motor outcome in children with CP (Ustad et al., 2009). Evidence suggests that physical therapy can improve functional possibilities for children, but is inconclusive as to which approach might be most beneficial (Mayston, 2001). The importance of early intervention (EI) has become widely recognized in the past few decades. Blauw-Hospers et al. describe early intervention as a multidisciplinary service provided to children from birth to 5 years of age to promote child health and well-being, enhance emerging competencies, minimize developmental delays, remediate existing or emerging disabilities, prevent functional deterioration, and promote adaptive parenting and overall family functioning (Blauw-Hospers and Hadders-Algra, 2005).

A systematic review on the effect of early intervention indicated that specific or general developmental programmes can have a positive effect on motor outcome after term age (Blauw-Hospers and Hadders-Algra, 2005). Preterm infants seemed to benefit more from intervention that aimed at mimicking the intrauterine environment (Blauw-Hospers and Hadders-Algra, 2005). Preliminary evidence also suggests that neonatal and early physical therapy may reduce the incidence of motor delay among infants born very preterm (Cameron et al., 2005). Trahan and Malouin found that short periods of daily physiotherapy, alternating with longer rest periods, seemed to optimize the effect of motor training compared to "physiotherapy as usual" in five children with severe CP, mean age 22.6 months (Trahan and Malouin, 2002). However, Ustad recently pointed out some of the challenges in evaluating early physical therapy intervention in children with CP. Treatment intensity, the treatment approach, optimal age for treatment, heterogeneity of children with CP, and differences in treatment compared with "physiotherapy as usual" are all questions that need to be further investigated (Ustad et al., 2009).

Processes associated with practice or experience that lead to relatively permanent changes in the ability to produce skilled actions are defined as motor learning (Thorpe and Valvano, 2002). In current paediatric physical therapy, motor skill acquisition is viewed as an active,

goal-directed process. This is a cognitive process requiring different levels of conscious attention depending on the task and the stage of learning (Thorpe and Valvano, 2002). Of primary concern to therapists is how best to facilitate learning to improve functional performance. Physical therapy is today often an established part of treatment programmes for children with CP.

CHAPTER 3: Evaluation of early motor function

A conceptual framework

Sherrington argued early in this century that motor behaviour is largely controlled by reflex mechanisms (Sherrington, 1910). He considered the reflex to be the fundamental unit of motor control and believed that physical events occurring in the environment served as the stimulus of action, triggering reflex circuits that were responsible for a movement response. In contrast to the reflex theories, hierarchical theories assume that all aspects of movement planning and execution are the sole responsibility of one or more cortical centres representing the highest command level within the hierarchy of the central nervous system (CNS). According to the theory, representations of movement are stored in memory in the form of plans or programmes for movement. Motor programmes activating different muscle synergies are located in the spinal cord and controlled from command centres in the brainstem. The neuronal networks are designed to handle the basic motor repertoire required for survival, including locomotion, posture, eye movements, breathing, chewing, swallowing and expression of emotions. The traditional reflex theories and hierarchical theories were supplemented by the dynamic system theory in the 1970s and 1980s. Dynamic system theory re-establishes a role for the environment as an important source of information for movement and action. It emphasises developmental change as multicausal involving the context, perception, action, and the role of exploration and selection in the emergence of new motor behaviour (Turvey, 1990, Thelen, 1995).

Today, the understanding of fetus and infant motor function has resulted in a gradual shift from the concept that motor behaviour is largely controlled by reflex mechanisms towards the notion that motility is the net result of the activity of complex spinal or brainstem machineries, which are subtly modulated by segmental afferent information and ingeniously controlled by supraspinal networks (Hadders-Algra, 2007). Motor control of rhythmical movements like locomotion, respiration, sucking and mastication are based on so-called central pattern generators (CPGs) (Hadders-Algra, 2007). De Graaf-Peters et al. characterize the development of the human brain as a protracted, neatly orchestrated chain of specific ontogenetic events. This comprises events like cell proliferation and neural migration, the role of the subplate as a transient structure for axonal routing to and from the cortex, neuronal differentiation and synapse formation, the formation of myelin, and regressive phenomena or so-called programmed cell death (de Graaf-Peters and Hadders-Algra, 2006). De Graaf et al.

also highlight the fact that the neural ontogenetic timetable has the age-specific nervous system and the age-specific motor function as a consequence, implying clinical consequences about age-specific characteristics affecting the way in which neural dysfunctions are expressed through movements.

The subplate is a transient neural structure which lies between the periventricular white matter and the developing cortical plate. The subplate is described as having a function as a "waiting room", a temporary goal of afferent fibres heading for a cortical destination (de Graaf-Peters and Hadders-Algra, 2006). This is further underlined by Hadders-Algra, raising the hypothesis that complexity and variation of movements by fetuses and preterm infants are brought about by the transiently present cortical subplate and that abnormal movements are the result of damage or dysfunction of the subplate and its efferent motor connections in the periventricular white matter. Hadders-Algra argues that the subplate has an important role in transmitting information to the central-pattern-generator (CPG) networks. Further, the dissolution of the subplate is regarded as playing an important role in the major developmental transformation occurring around 3 months post term age: the spontaneous motor activity in the infant is replaced by goal-directed motor activity. The conceptual changes in motor function in the fetus and young infant, implying central pattern generators subtly modulated and controlled by supraspinal networks, have been paralleled by changes in ideas on motor development and neurological assessment of young children (Hadders-Algra, 2007).

Assessment of early motor function

Recognition of the need for methods for assessing early motor function has increased due to a number of recent events: 1) increasing interest in the effects of various environmental toxins on the fetus and infant; 2) recognition that all drugs used by pregnant mothers and neonates should be evaluated for effects on the developing CNS; 3) limitations in societal resources that necessitate identification of the highest risk infants for comprehensive neurodevelopmental follow-up and early intervention services (Allen and Lipkin, 2005). It is well-known to developmental clinicians that abnormal or suspect motor function observed in very young infants may "normalize" or may appear to follow very different developmental trajectories. Hence, there is a need for early information and feedback about CNS development through assessment of motor function in preterm infants, full-term neonates, and young infants.

Besides technical assessment techniques like cerebral ultrasound (CUL), magnetic resonance imaging (MRI) and computer tomography (CT) that may show structural changes in the brain, there are various ways of evaluating neuromotor function in infancy. Physiotherapists, occupational therapists, and paediatricians play an important role in early detection of CP through the use of neuromotor function assessments techniques. Kirchner and Guyatt classified health measure instruments into three categories according to the goals they served. The first is discrimination which implies making a distinction between children who show features of deviant motor function compared with the general healthy population. The second goal is prediction; instruments are used as a diagnostic tool to predict developmental outcome. The third purpose is evaluation of longitudinal change of an individual over time (Kirshner and Guyatt, 1985). Instruments are generally validated for only one of the three goals (Heineman and Hadders-Algra, 2008)

Heineman and Hadders-Algra (2008) recently reviewed available methods for the evaluation of motor function in infancy, including 15 instruments. According to them, instruments for assessment of early neuromotor function are often chosen on the basis of habit and for practical reasons, and not on the basis of information regarding test accuracy and validity. The selected instruments in their review were systematically evaluated with a focus on population, age, descriptive/evaluative/predictive purposes, test construction and training required to become an assessor, and time needed to administer the test. Nine instruments available for professionals working in NICU follow-up programs for young infants are presented in Table 1 moderated from Heineman et al.. Only the two instruments that assess qualitative aspects of motor function (TIMP and GM assessment) showed good predictive validity with respect to later CP, and these are useful for infants under the age of 4 months (Heineman and Hadders-Algra, 2008).

Table 1. Description of instruments for the evaluation of neuromotor function in infancy, moderated from Heineman and Hadders-Algra (Heineman and Hadders-Algra 2008)

Assessment	Population	Age group	Purpose	Test properties/time
Touwen infant neurological examination (Touwen)	Infants	0 months-independent walking	Discriminative	Neuropaediatric: Posture, tone, reflexes / 15 min
Amiel-Tison neurological examination (Amiel-Tison)	At-risk infants	0-6 years	Discriminative	Neuropaediatric: Muscle tone, motor milestones, reflexes / 10 min
Hammersmith infant neurological examination (HINE)	Infants	2-24 months	Discriminative Predictive	Dubowitz and Dubowitz method for neurologic assessment / no data available
Infant neurological International battery (Infanib)	At-risk infants	1-18 months	Discriminative	Neuromotor behaviour: spasticity, head and trunk control, resting tone / no data available
Bayley scales of infant development (BSID-II/III)	Children	1 months-3.5 years	Discriminative Evaluative	General maturationalist principles / 25-60 min
Peabody developmental motor scales (PDMS-II)	Children	0-6 years	Discriminative	Gross and fine motor scales subtests: reflexes, stationary, locomotion, object manipulation, grasping and visual-motor integration / 40-60 min
Alberta infant motor scale (AIMS)	Infants	0 months-independent walking	Discriminative	Sequential development of postural control relative to four postural positions / 15 min
Test of infant motor performance (TIMP)	Infants	Birth (32 wks PMA)-4 months	Discriminative	Items from neurological, neurobehavioral and motor assessments / no data available
General movement assessment (GM assessment)	Infants	Birth-5 months	Discriminative Predictive	Neural group selection theory principles / 3 min video

In general, important limitations of assessments of early neuromotor function are that they are unable to accurately identify which infants are manifesting true, persisting developmental deficits as opposed to delays that will resolve over time. The clinical evaluations of early development are used to target those at risk for developmental disability, but the consistently high rate of false positives limits this clinical applicability in terms of accurate early identification (Hadders-Algra, 2001, Majnemer and Snider, 2005).

General movement assessment

One of the most fundamental new insights in developmental neurology during the last 40 years is the concept of ontogenetic adaption with its consequences. This concept highlights the fact that during the development and change of the individual brain the motor functional repertoire of the neural structures must meet requirements of the organism and its environment (Prechtl, 2001). The developing organism is adapted to the internal and external requirements. Age-specific difference of the developing nervous system gives age-specific nervous tissue vulnerability and age-specific motor function which requires age-adequate assessment procedures (Prechtl, 2001). Today it is acknowledged that infant spontaneous motor activity expresses the spontaneous neural activity, and is therefore an excellent marker of brain lesions (Prechtl, 2001).

General Movements

The young human nervous system continually generates a variety of movement patterns. In the human fetus, isolated limb movements, twitches, stretches, yawning and breathing movements emerge at 9 to 12 weeks postmenstrual age. These generated movement patterns continue after birth, irrespective of when birth occurs (Einspieler and Prechtl, 2005). During the course of development one movement pattern appears for the functional assessment of the young nervous system. General Movements (GMs) are complex, occur frequently, and last long enough to be observed properly. They 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 directions of movements make them fluent and elegant and create the impression of complexity and variability (Prechtl, 1990). Before term GMs are referred to as Preterm GMs, at term age until 6 to 9 weeks post term age they are called Writhing Movements. At 6 to 9 weeks post term age fidgety GMs appear. Fidgety movements are

Change of general movement quality

General movements change their quality if the nervous system is impaired (Einspieler and Prechtl, 2005, Einspieler et al., 2004). Abnormal GMs are characterized by a reduced complexity and reduced variation (Prechtl, 1990, Ferrari et al., 1990, Hadders-Algra, 1993, Prechtl et al., 1993, Hadders-Algra, 1996, Prechtl et al., 1997, Einspieler and Prechtl, 2005, Einspieler et al., 2004). They lack fluency and have an abrupt onset (Hadders-Algra, 1996). The difference in low-risk and high-risk infants or brain-damaged infants is not present with respect to the rate of GM occurrence, i.e., their quantity (Ferrari et al., 1990, Einspieler and Prechtl, 2005, Einspieler et al., 2004).

Abnormal general movements

According to the Prechtl approach, abnormal GMs either have a poor repertoire, are cramped-synchronized, or are chaotic (Einspieler and Prechtl, 2005, Einspieler et al., 2004). Fidgety movements can be either abnormal or absent. All normal and abnormal patterns of GMs are demonstrated by a video (Einspieler et al., 2004). The approach developed by Hadders-Algra distinguishes between four classes of GM quality: two forms of normal GMs, normal-optimal and normal-suboptimal GMs; and two forms of abnormal GMs, mildly and definitely abnormal GMs (Hadders-Algra, 2004).

The Prechtl approach has the following subcategories related to abnormal general movements:

Poor-Repertoire GMs (PR)

Poor-Repertoire sequences of successive movement components are monotonous and movements of the different body parts do not occur in the complex way seen in normal GMs (Ferrari et al., 1990, Einspieler and Prechtl, 2005). The predictive value for CP of poor repertoire GMs is rather low (Einspieler et al., 2004).

Cramped-Synchronized GMs (CS)

These abnormal movements appear rigid and lack the normal smooth and fluent character, all limbs and trunk muscles contract and relax almost simultaneously. If Cramped-Synchronized GMs are observed consistently during a number of weeks, this is of high predictive value for the development of spastic CP (Einspieler and Prechtl, 2005, Einspieler et al., 2004, Ferrari et al., 1990).

Chaotic GMs (Ch)

Chaotic GMs are movements of large amplitude of all limbs and occur in a chaotic order without any fluency or smoothness. They consistently appear to be abrupt (Ferrari et al., 1997, Einspieler and Prechtl, 2005, Einspieler et al., 2004).

Abnormal Fidgety Movements (Fa)

Abnormal fidgety movements look like normal fidgety movements, but their amplitude, speed, and jerkiness are moderately or greatly exaggerated. Abnormal fidgety movements are rare and their value in predicting CP is low (Einspieler and Prechtl, 2005). Abnormal fidgety movements have been discussed in the context of the development of mild neurological deficits (Einspieler et al., 2007, Hadders-Algra et al., 2004, Hadders-Algra and Groothuis, 1999, Bruggink et al., 2008, Bouwstra et al., 2009). Some findings demonstrate a relationship between "mildly abnormal GMs" at the age of 3 to 4 months with increased risk for the development of minor neurological deficits, attention deficit hyperactivity disorder, and boisterous, disobedient behaviour of 4- to 9-year-old children (Hadders-Algra and Groothuis, 1999). The classification "mildly abnormal GMs" does not exist in Prechtl's GM assessment, but only in the Hadders-Algra approach to GM assessment (Einspieler and Prechtl, 2005). Within the Prechtl approach, there have been some studies using a reliable (Fjortoft et al., 2009) detailed quantitative score called the Assessment of Motor Repertoire – 3 to 5 Months. One study found no relationship between a detailed score of poor repertoire general movements and normal outcome (Nakajima et al., 2006). Another study found some relationship between details in the early motor repertoire and minor neurological dysfunction at school age (Bruggink et al., 2009) and one study reported no association between finger movements and finger postures and brain damage (Konishi and Prechtl, 1994). Recently, mildly abnormal general movements identified by means of the Hadders-Algra approach in three-month-old infants have shown to have a prevalence of 25% in a general population (Bouwstra et al., 2009).

Absence of Fidgety Movements (F-)

The Prechtl approach classifies FMs as absent or present (Einspieler et al., 2004). If fidgety movements are never observed from 9 to 20 weeks post-term age, they are called abnormality "absence of fidgety movements". The absence of fidgety movements is highly predictive for later neurological impairments - particularly for CP, demonstrating sensitivity values of 80 to 100% (Prechtl et al., 1997, Einspieler et al., 2002, Adde et al., 2007, Einspieler et al., 1997,

Seme-Ciglenecki, 2003, Einspieler et al., 2004, Einspieler and Prechtl, 2005, Hadders-Algra, 2004, Stahlmann et al., 2007).

Figure 4 illustrates different outcome paths by GM assessment classification from a longitudinal study on 130 infants with various ultrasound findings adapted with permission from Einspieler et al. (Einspieler et al., 2004) and the Mac Keith press.

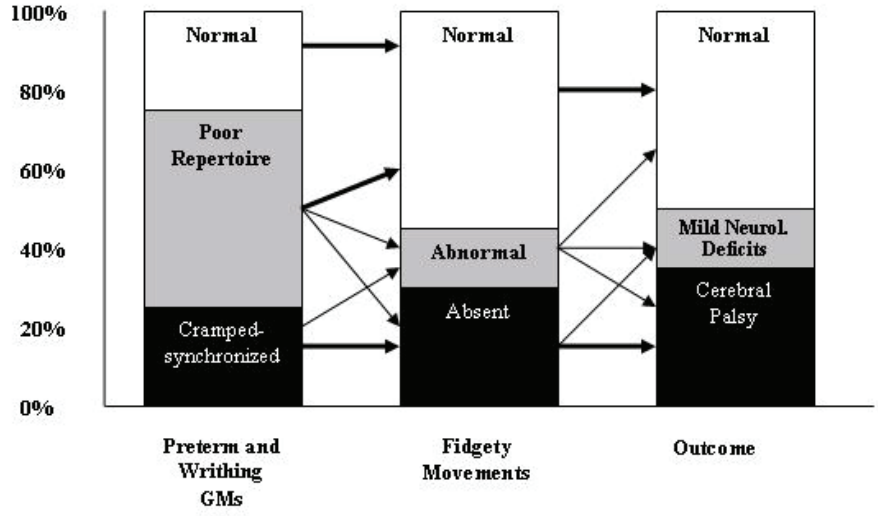

Figure 4: A longitudinal study on 130 infants with various ultrasound findings: preterm and writhing quality (left) preceding the quality of fidgety movements (middle), which is predictive for the neurological outcome at three years. Adapted with permission from Christa Einspieler (Einspieler et al., 2004) and the Mac Keith Press.

GM assessment classification: Appraisal of movement quality by Gestalt perception

GM assessment is identical for the different periods during which GMs can be observed, i.e. during fetal life, the preterm period, and the first months after term age. The technique is based upon the appraisal of the quality of spontaneous movements by the means of Gestalt perception (Hadders-Algra, 1996). The global Gestalt perception is a complex brain process enabling the evaluation of complex phenomena (Lorenz, 1971). In the case of GM assessment, this is the complex task of evaluation of the complexity of GMs. Gestalt perception allows the evaluation of the repertoire of movement patterns displayed by all parts of the body and does not pay special attention to particular behaviour of specific body parts (Hadders-Algra et al., 2004).

Training required

The basic principles in the Hadders-Algra approach can be learned in 2 days. Further practice with approximately 100 GM recordings is required to become a skilled observer (Hadders-Algra et al., 2004). In the Prechtl approach, standardized basic and advanced training courses, lasting 4 to 5 days, are provided by the General Movement Trust (http://www.general-movements-trust.info). Completed training courses enable professionals in the field of infant and child neurology to apply Prechtl's GM assessment accurately (Einspieler and Prechtl, 2005).

General movement assessment - strengths, benefits and limitations

Persistently abnormal GMs as well as the absence of "fidgety" characteristics at the fidgety movements age indicate a serious risk for the development of handicap (Hadders-Algra, 2004). The GM assessment technique predicts later CP at much earlier age than was previously possible (Einspieler and Prechtl, 2005). Further, normal fidgety movements are an excellent marker for a normal neurological outcome (Prechtl et al., 1997). In addition, the qualitative assessment of GMs is non-intrusive and cost effective.

However, the assessment of GMs has several limitations. It is subjective and any kind of environmental stimulation or disturbance might interfere with the observer's Gestalt perception and should be avoided. The assessor should never assess for more than 45 minutes because of possible disturbing tiredness. The observer must be experienced, with completed courses or training, but no requirements for maintaining observation skills are described. It can also be argued that for clinicians working alone, assessment of movement qualities according to GM assessment might be difficult to trust (Adde et al., 2007). The two existing approaches have different terminology, interpretation of movement qualities and classification and may confuse clinicians who are not experts in the field. Furthermore, the GM assessment is limited in use in ordinary clinical practice outside Europe (Garcia et al., 2004).

Human motion analysis

Motion capture, motion tracking, or "mocap" are terms used to describe the process of recording movement and translating that movement into a computer-based digital model. It is used in military, entertainment, sports, and medical applications. In medical science, new motion capture technologies have made it possible to perform quantitative analyses of movement and thereby a possibility to discriminate normal versus pathological movement on

the basis of objective criteria. The methods and systems cover optical systems that triangulate the 3D position of a subject between cameras, mechanical motion capture systems that directly track body movements, and magnetic systems that calculate position and orientation of body parts using transmitters and receivers (Jensenius, 2009). During the last decade, there have been studies investigating infant movement by the use of motion capture. Fallang and colleagues investigated the total body centre of pressure during reaching tasks performed by pre-term and full-term infants by the use of a force plate (Fallang et al., 2003). Properties of motor activity in healthy newborns were studied by Grunt and colleagues using a low weight, high precision accelerometer (Grunt et al., 2009), and a computer-aided approach for differentiation of GMs using an electromagnetic tracking system (ETS) has recently been reported (Kim et al., 2009). Lower-extremity movements in infants were studied by van der Heide and co-workers using 2D video recordings and markers on the lower extremities (van der Heide et al., 1999) and 3-dimensional acquisition with video cameras and reflector markers has been performed for detection of newborns at risk for developing spasticity by Meinecke et al. (Meinecke et al., 2006). However, all the methods mentioned are cumbersome in use and restricted to laboratory settings because of the need for comprehensive instrumentation and advanced analyses. They are therefore, so far, out of range for ordinary clinical practice

Computer Vision

Computer vision is the technology of machines that see and obtain information from images. It can also be described as a complement to biological vision. The interest from computer vision researchers in human motion analysis during the last decade is motivated by a wide spectrum of applications, such as athletic performance analysis, surveillance, human-machine interfaces, and video conferencing (Aggarwal and Cai, 1998). Another prominent application field is medical computer vision or medical image processing. This area is characterized by the extraction of information from image data for the purpose of medical diagnostics. An example of information which can be extracted from such image data is detection of tumours, arteriosclerosis or other malign changes. This application area also supports medical research in magnetic resonance imaging (MRI) techniques by providing new information, e.g., about the structure of the brain.

Human motion analysis by computer vision techniques concerns the detection, tracking and recognition of people, and more generally, description and understanding of human

behaviours, from image sequences involving humans (Wang et al., 2002). Video analysis of human dynamics, in particular, has become an important area of research devoted to understanding human dynamic physical behaviour in a complex environment. This is related to the tracking of body parts such as the face, hands, fingers, legs, etc., and modelling motion behaviour using motion analysis (Wang and Singh, 2003). Further, the possibility of vision-based human motion analysis without markers has the potential to provide an inexpensive, non-obtrusive solution for the estimation of body positions. Vision-based motion capture systems provides such solutions, using cameras as sensors and no instrumentation of the person studied (Poppe, 2007).

Computer vision applications in human motion capture can roughly be grouped under three titles: *surveillance*, *control* and *analysis* (Moeslund et al., 2006). *Surveillance* applications are related to monitoring locations where a large number of people pass through such as airports and subways. *Control* applications estimate motion or pose parameters and are used to control something. This is typical in virtual reality or the entertainment industry. *Analysis* applications might be automatic diagnostics of, for example, orthopaedic patients or analysis and optimization of athletes' performances (Moeslund et al., 2006). The number of potential applications, the scientific complexity, the speed and price of current hardware are all factors that recently have intensified the effort within the computer vision community towards automatic capture and analysis of human motion (Moeslund et al., 2006).

The Musical Gesture Toolbox

Within the field of analysis of music-related movements it has been demonstrated that novices and experts alike tend to spontaneously associate sound features with specific actions (Jensenius et al., 2005, Jensenius, 2009). Such spontaneous action-sound couplings are based on massive, life-long experience, and may be a valuable source of competence that can be investigated. For this reason, Jensenius and co-workers have recently performed a series of studies of music-related actions. Using modern computer vision techniques they have developed tools for studying music-related movements within the MAX/MSP/Jitter software environment (Jensenius et al., 2005). The main goal of making their *Musical Gesture Toolbox* was to create computer-based tools that would help in studying movement, action and gesture with respect to the corresponding sound. Care was taken to make the tools flexible so that they could also be used with related software for video analysis (Jensenius, 2009).

The Musical Gesture Toolbox contains a number of modules with different functions. A *source* module makes it possible to import video directly from a connected DV or web camera, and to play back any QuickTime-readable video file. The toolbox gives easy access to scrubbing functions and allows study of movements in slow motion. An *adjustment* module allows for changing brightness, contrast and cropping (Jensenius et al., 2005). It is also possible to use the crop function to focus on a specific part of the image. The *motion* module can display or visualize different video quantities such as quantity of motion and the centre of gravity in the image (to be described more closely in Chapter 7, page 58). These features are particularly interesting for qualitative observations, since they enhance movements that are not so easily seen in the original video. Finally, the *output* module outputs running quantitative data values representing the movement in the video stream (Jensenius et al., 2005). These data can be saved to a text file and allow further analysis in software like Excel and the Statistical Package for the Social Sciences (SPSS). The Musical Gesture Toolbox makes it possible to have many different visual representations and graphs of movement qualities in addition to deriving quantitative movement data. The *motiongram* is such a visual representation developed by Jensenius.

Motiongram

Jensenius studied movements of musicians and dancers by the use of one single stationary camera. He needed tools to visualize movement-related information from video material for qualitative observations. A traditional timeline display and a motion history display, like those by Eadweard Muybridge in the late 18th century (Figure 5), display the content of scenes rather than movement-related information. They do not reveal the actual *motion* in the sequences (Jensenius, 2006).

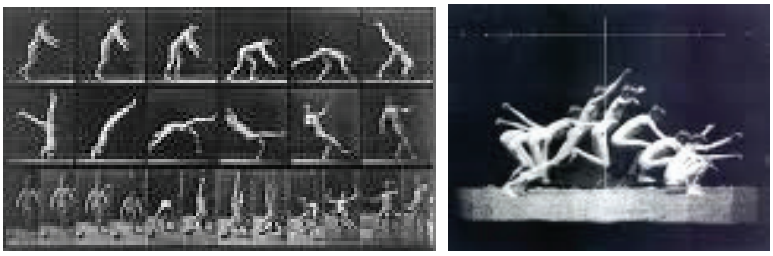

Figure 5: A traditional timeline display (left) and a motion history image (right) made of Eadweard Muybridge (1830-1904). (Available from http://www.americanhistory.si.edu/muybridge/)

By calculating the differences between corresponding pixels in consecutive frames in a video stream, Jensenius and co-workers created a *motion image*. The motion image can be further transformed into a *motiongram*. The motiongram displays the level and location of motion in the video sequence, and makes it easy to observe movement trajectories over time (Jensenius, 2006) (Figure 6).

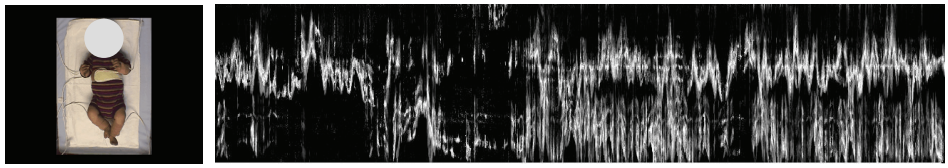

Figure 6: Infant with a motiongram display from a video sequence. Arm movements are displayed in the upper part and leg movements in the lower part of the motiongram. Time is running from left to right.

The General Movement Toolbox

For the purpose of studying GM qualities, the Musical Gesture Toolbox developed by Jensenius and co-workers was customized as the General Movement Toolbox (GMT). This was done by making some changes in the graphical user interface and removing some software modules.

CHAPTER 4: Method development and evaluation

Prognosis and prognostic research - What, why and how?

Prognosis can be defined as foreseeing, predicting, or estimating the probability or risk of future conditions. In medicine, prognosis relates to the probability or risk of an individual developing a particular health outcome over a specific time, based on a clinical profile. Outcomes are often events like death, disease or disease progression (Moons et al., 2009b). A single predictor or variable rarely gives an adequate estimate of prognosis. Often, multiple predictors are used to estimate a patient's prognosis. To provide outcome probabilities for different combinations of predictors, tools called prognostic models, prediction rules, or risk scores are developed (Moons et al., 2009b).

Prognostic models in medicine are used in various settings and for various reasons. Firstly it is important to inform individuals about the future course of their illness and to guide doctors, physiotherapists and patients (or parents) in joint decisions on further treatment. Secondly, a prognostic model is important in selecting relevant patients for therapeutic research. For example, prognostic models for CP development may be used to select young infants for a randomized trial of early physiotherapy intervention. Predicting outcome is not synonymous with explaining their cause. In aetiological research, the focus is on explaining whether an outcome can be attributed to a specific risk factor. In prognostic research, the focus is on predicting future outcome, and it is neither an aim nor a requirement to explain causality (Moons et al., 2009b). Third, prognostic models can be used to compare differences in performance between hospitals or treatment units. For example, the clinical risk index for babies (CRIB) was developed to compare performance and mortality among neonatal intensive care units (Cockburn et al., 1993).

There are three major steps in prognostic research: developmental studies, validation studies and impact studies. Developmental studies develop a prognostic model, including identification of the important predictors, assigning relative weights to each predictor, and estimating the models predictive performance. Validation studies validate the developed model's predictive performance in new participants and impact studies quantify how much the prognostic model improves decision making and patient outcome. The best study design in prognostic research is a prospective study as it enables optimal measurements of predictors and outcome. Studied predictors should be clearly defined, standardized, and reproducible to

enhance generalizability and application of study results to practice (Moons et al., 2009b). The multivariable character of a developing study makes it difficult to estimate the required sample size. When the number of predictors is higher in relation to the number of outcome events, there is a risk of overestimating the performance of the model. Studies have suggested that at least 10 events are required for each candidate predictor (Moons et al., 2009b).

Moons et al. say that application of a prognostic model requires a method or instrument feasible for clinical use. Prognostic models are not meant to take over the job of the doctor or physiotherapist. They are intended to help health professionals make decisions by providing more objective estimates of probability as a supplement to other relevant clinical information and test results. Furthermore, they improve understanding of the determinants of the course and outcome of patients with a particular disease (Moons et al., 2009b).

Evaluation of an assessment instrument

Validity

An assessment instrument and a prognostic model should have good validity and reliability. Validity is often defined as the extent to which an outcome measure actually measures what it purports to measure (Elasy and Gaddy, 1998). Validity issues include reliability, criterion validity comprising concurrent validity (convergent and divergent validity) and predictive validity, and construct validity with discriminative ability. Convergent validity is the degree to which the instrument is concurrent with the "gold standard" and divergent validity is how different it is from other assessment instruments. The construct validity is evaluated by correlating it with the most accurate existing test, a "gold standard" (Elasy and Gaddy, 1998). Discriminative ability reflects the extent to which the assessment instrument differentiates among the patients for whom the measurements are being applied and the predictive validity is how well a correct later outcome is predicted.

Reliability

Reliability is commonly defined as the degree to which test scores are free from measurement errors. Components of reliability are instrument reliability, rater reliability comprising intra-rater and inter-rater reliability, and test-retest reliability. The intra-rater reliability is the degree of consistent results from measurements provided from one rater on different occasions. The inter-rater reliability is the degree of consistent results from measurements provided by different raters on the same objects at the same time. Finally, the test-retest

reliability is based on parallel assessments of patients on different occasions. A reliable instrument provides a measure that is precise and accurate. The goal is to have an outcome or an instrument that yields a small difference between replicated measurements on a patient who truly has not changed (test-retest reliability). No measure can have a higher correlation with other measures than with itself. Therefore a reliable measurement must show consistency. A measurement error originating from an instrument can be random or systematic. Random errors do not affect the average of the measurements, but only the variability around the average. Systematic errors do affect the average and is often called bias.

Sensitivity and specificity

The best test is commonly referred to as the "gold standard". An alternative test might be developed to overcome problems with a "gold standard". For example, the best test for CP diagnosis is to assess the child at 4 years of age. However, to overcome this length before diagnosis an alternative early prognostic test might be developed. The quality of such a test is judged by its sensitivity and specificity. Results from a test have four possible interpretations: two correct (or true: true negative and true positive) and two incorrect (or false: false negative and false positive). Sensitivity is defined as the proportion of patients with the disease who have a positive test. Specificity is defined as the proportion of patients without the disease who have a negative test. For a test to be accurate, it must be both highly sensitive and highly specific (Chu, 1999). When a test is performed, sensitivity and specificity do not indicate whether a positive result truly means the presence of disease. That information is given by the positive and negative predictive values. The positive predictive value (PPV) is defined as the proportion of infants with a positive test that has the disease. Negative predictive value (NPV) is defined as the proportion of infants with a negative test that do not have the disease (Chu, 1999)

External validation of a prognostic model

A requirement of a multivariable prognostic model is transferability, or external validity - that is, confirmation that the model performs as expected in new but similar patients (Royston et al., 2009). Various factors may cause a prognostic model to perform poorly when applied to other patients. These could be deficiencies in the design of modelling methods, the absence of important predictors and differences in patient characteristics in the new samples. Further, external validation studies are necessary because performance related to the original data may well be optimistic. A prognostic model is "a snapshot in place and time, not fundamental

truth" (Altman et al., 2009). It is crucial to quantify the performance of a prognostic model on new series of patients, ideally in a different location, before applying the model in daily practice to guide patient care.

CHAPTER 5: Aims of the thesis

The assessment of the quality of GMs is a sensitive tool to evaluate brain function in young infants when used by experienced observers. The GM assessment technique is limited in use in clinical practice possibly due to the expert knowledge needed. Motion capture advances have made it possible to capture both movement quantities and display movement qualities from 2D video recordings. These facts have motivated us to perform four studies further presented in this thesis.

The overall aim of this thesis is to increase knowledge about GM assessment and prediction of CP used in a clinical setting, to increase knowledge about infants with or without fidgety movements by quantitative features, and to develop a new computer-vision-based prognostic model for prediction of CP in young infants. The specific aims were to:

- test GM assessment inter-rater reliability for fidgety movement *(Paper I)*
- verify the GM assessment for prediction of CP (*Paper I)*
- identify movement characteristics that discriminate between infants with and without fidgety movement using a computer-based GM expert system *(Paper II)*
- identify movement characteristics that discriminate between infants with and without fidgety movements using a computer-vision-based toolbox *(Paper III)*
- develop a discriminative computer-vision-based model for identification of infants with absent and present fidgety movements *(Paper III)*
- develop and evaluate a prognostic computer-vision-based model for prediction of CP *(paper IV)*
- develop and evaluate a prognostic computer-vision-based model for prediction of function in children with CP *(Paper IV)*

CHAPTER 6: Studies included in the thesis

Included in this thesis are four studies based on data from the same population of young infants. Four slightly different samples were composed, according to different research questions. The studies included infants from Norway from the period 2002-2004, at high and low risk for CP development, with different age at outcome measurement. The infants were monitored as follows:

- Low and high risk infants assessed using GM assessment at 2 to 5 months corrected age and followed up until they were 2 years old (Study I, n=74)
- Low and high risk infants assessed using GM assessment and kinematic measurements at 2 to 5 months corrected age (Study II, n=14)
- Low and high risk infants assessed using GM assessment and the computer-vision-based assessment instrument at 2 to 5 months corrected age (Study III, n=82)
- High risk infants assessed by the computer-vision-based instrument at 2 to 5 months corrected age and followed up until they were 5 years old (Study IV, n=30)

Design

In accordance with the different aims of the studies, different study designs and samples were used in the four studies. Table 2 gives an overview of the different study samples included and the progress through the four studies presented in this thesis. The study designs were as follows:

Study I

Study I was a prospective clinical study and a reliability study investigating both inter-rater reliability of the GM assessment technique and the GM assessment for the prediction of CP. This was performed by assessing general movements from the fidgety movement period by two observers, and assessing CP status at 2 years of age. The inter-rater reliability of fidgety movement classification was evaluated and the accuracy in CP prediction was tested.

Study II

Study II was the first step in a method developmental study. Kinematic measurements were performed in a small sample of infants and an interdisciplinary qualitative approach was used to elicit expert general movement knowledge for the identification of objective features characteristic of fidgety movements. The study generated hypotheses on possible quantitative

features relevant to the study of fidgety movements. The study used a software named Enhanced interactive general movement assessment (ENIGMA).

Study III

Study III was the second step of a method development study and was a discriminative study. GM qualities with respect to present or absent fidgety movements were described by means of different qualitative displays generated by the computer-vision-based instrument. Identification of possible quantitative predictors was performed and concurrent validity of absent and present fidgety movements was evaluated.

Study IV

Study IV was the third step of the method development. Study IV used a prospective study design following the infants until they were 5 years of age. A prognostic model was developed and prediction of CP was evaluated.

Table 2. Overview of the samples and time of assessment in the four included studies.

	Sample	Assessment	Outcome
Study I	Low and high risk infants, n = 74: • 49 low risk • 25 high risk Consent was requested for 83 infants: 79 responses - 4 for which consent was declined - 1 no data available = 74	10 -18 weeks post term age	2 years
Study II	Low and high risk infants, n = 14 : • 7 low risk • 7 high risk 14 infants with 15 recordings selected from the sample in study I.	10-18 weeks post term age	10-18 weeks post term age
Study III	Low and high risk infants, n = 82 • 49 (study I) + 1 = 50 low risk • 25 (study I) + 7 = 32 high risk 74 consents from study I + 8 asked for consent and approved = 82	10-18 weeks post term age	10 - 18 weeks post term age
Study IV	High risk infants, n = 30 34 consent requests (32 from study III, 2 from study I) 34 responses - 3 for which consent was declined - 1 excluded due to syndrome affecting motor function = 30	10 - 15 weeks post term age	5 years

CHAPTER 7: Materials and methods

Subjects

The overall aim of this thesis was to develop a new computer-based method for prediction of CP in young infants. Study infants were included on the basis of presumed high risk of CP development in addition to the inclusion of normal infants to the control group. Of 83 letters sent to parents for informed consent in study I during the period 2002-2004, 79 parents answered. Four families did not consent. The remaining 75 parents approved participation in the 2-year follow-up study (study I). After approval, letters were sent to the family physician and the public health nurse for collection of neurological outcome status of the children (appendix 2); 74 answers were returned. Thus, the final study population for study I consisted of these 74 infants. In study II, 14 infants from study I were selected. The selection was designed to represent differences in high and low risk, birth weight, gestational age, and sex, and in particular to ensure a representative broad span of different movement patterns for observation of GMs. In study III, the parents of 8 additional infants were asked to participate and they all gave their consent. The final study population for study III then consisted of these 82 infants. Hence, the subjects included in studies I, II and III are convenience samples of preterm and term infants at low or high risk of neurological impairment. In study IV, only high risk infants were included. In this study 34 letters of invitation were sent to parents (most of whom participated in study I and III); consent was not granted in three cases and one infant was excluded because of a syndrome affecting motor function. The final study population for study IV thus consisted of 30 high risk infants.

The majority of infants enrolled were from St. Olavs Hospital in Trondheim, Norway. High risk infants, both term and preterm, as well as low risk preterm infants were included from the neonatal intensive care unit, whereas healthy term infants were included from the maternity ward. Nine high risk infants were included from four other hospitals in the southern part of Norway. High risk infants were included on the basis of the medical history and cerebral ultrasound results. Children were classified as being at high risk if they had one or more well-known perinatal risk factors for neurological impairment. Table 3 describes the inclusion criteria for the studies and Table 4 lists the baseline characteristics of the included infants. Infants with congenital syndromes and malformations that could interfere with their spontaneous movements were excluded from the studies.

Table 3. Inclusion criteria for infants in *Study I-IV*

Study population study I / III	**Eligibility criteria**[a]	**Paper**
Preterm and term infants at low or high risk of neurological impairment	*High risk infants:* 1) Perinatal stroke 2) Perinatal asphyxia 3) Intra-/peri-ventricular hemorrhage (IVH/PVH), grade III or IV 4) Severe hypoglycaemia and E. coli sepsis 5) BW<1000 g and/or GA<28 weeks 6) Bronchopulmonary dysplasia with suppl. O_2 at discharge *Low risk infants:* 1) BW>1000 g and/or GA>28 weeks 2) No pre-or postnatal complications *Video recording:* 1) At least one video recording from the fidgety movement period available	I/III
Study population study II	**Eligibility criteria**[a]	
Preterm and term infants at low or high risk of neurological impairment	*High and low risk infants:* 1) Criteria as for study I and III *Video recording:* 1) Video recording from the fidgety movement period available 2) Representing a broad span of movement patterns judged by a GM expert	II
Study population study IV	**Eligibility criteria**[a]	
Preterm and term infants at high risk of neurological impairment	2) Criteria for high risk infants as for study I and III 3) At least one video recording from the fidgety movement period available with correlating GM assessment classification	IV

[a] To be included one or more criteria had to be fulfilled

Table 4. Baseline characteristics for infants included in *Study I-IV*

Study	I GM assessment -reliability and prediction of CP at 2 years of age	II Enhanced interactive general movement assessment	III Computer-vision -based detection of FMs	IV Computer-vision -based prediction of CP at 5 years of age
Paper	I	II	III	IV
Infants: n	74	14	82	30
Video recordings: n	135	15	137	30
Gender: male numbers (%)	33(45)	7(50)	37(45)	17(57)
Preterms (%)	42(57)	8((57)	48(58)	23(77)
High risk/low risk: n	25/49	7/7	32/50	30/0
Preterm birth weight (g): median	1367	2006	1910	
Preterm gestational age (weeks): median	30	34	29	

The procedures followed in the four studies were in accordance with the ethical standards of the regional committee on human experimentation and with the Helsinki Declaration. Written consent was obtained from all parents and The Regional Committee for Medical Research Ethics, and Norwegian Social Science Data Services approved the studies.

Methods

Video recordings and editing

The videos were recorded using a Sony DCR-PC 100E camera in all four studies. Video recordings were in accordance with the detailed instructions provided by Prechtl and co-workers for making a reliable GM assessment (Einspieler et al., 2004, Einspieler and Prechtl, 2005). All video recordings were performed within the fidgety movement period, 10-18 weeks post-term age. The recordings were repeated several times (range 1-5) to ensure that the quality of GMs (normal or abnormal) could be accurately judged by the observer. In Study IV, one recording closest to week 13 post term age, which is the age at which the fidgety movements normally come to full expression, was chosen for each participating infant.

Because the infant's movements were also analysed using 3D electro-magnetic sensors for study II, all infants had motion tracking sensors attached to each extremity, on the sternum and on the forehead (MiniBIRD, Ascension Technology Corporation, Burlington, VT, USA).

In addition to the Prechtl instructions for video recordings we made a standardized mobile laboratory setting to provide a fixed and general camera position in all recordings. This included the use of a standard mattress, using a stationary digital video camera at a fixed distance of 110 cm above the infant. Figure 7 illustrates the standard context in which all recordings were performed in our studies.

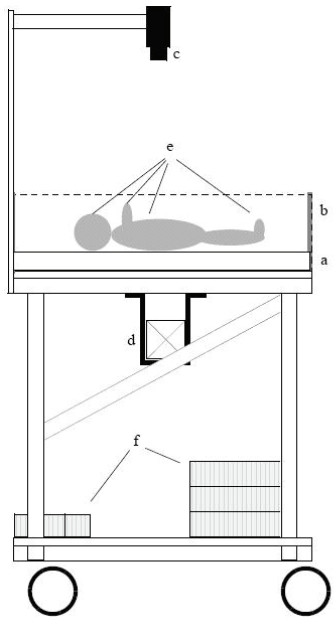

Figure 7: A mobile data acquisition set-up. The infant was placed on a mattress (a) with rigid, transparent walls (b) and an overhead video camera (c) (used in all studies). Motion tracking was carried out by means of a magnetic field transmitter (d) mounted under the mattress and magnetic sensors (e) attached to relevant body parts of the infant (study II). Power supply and control electronics (f) for the motion tracking system were mounted on the base of the set-up in order to lower the centre of gravity (for stability) (Drawing: Ø. Stavdahl).

Recordings were performed at least 30 minutes after feeding during active wakefulness. The infants were partly dressed with body vest and nappy, lying supine. The size of the mattress was large enough to ensure sufficient space to move freely. As recommended by both Prechtl and Hadders-Algra, care was taken to ensure a neutral environmental temperature that was comfortable (24-28 ^{o}C) (Einspieler et al., 2004, Hadders-Algra, 1996, Hadders-Algra, 2004). Behavioural state affects the form of the GMs (Hadders-Algra et al., 1993). The optimal state for GM analysis is active wakefulness, behavioural state 4 (Hadders-Algra, 2004, Einspieler et al., 2004, Einspieler and Prechtl, 2005). Efforts were therefore made to carefully optimize the best behavioural state for the infant during the recording session. After term age, it is usually best to record movement activity during 10-15 minutes (Hadders-Algra, 2004, Einspieler and Prechtl, 2005). All video recordings in our studies therefore lasted 10-20 minutes.

According to Hadders-Algra and Prechtl, movements elicited by external stimulation, disturbed by happenings in the environment or present during crying or non-nutritive sucking should be excluded from the analysis (Einspieler and Prechtl, 2005, Hadders-Algra et al., 2004). Therefore, all video recordings were reviewed by a trained GM assessment observer and if necessary edited. In accordance with the Prechtl method, recordings were edited to ensure several minutes containing representative GMs in the correct behavioural state 4. The same edited recordings were carefully checked once again for study IV, ensuring sequences of 1-5 minutes in length with the correct behavioural state for the computer-based assessment.

General movement assessment (studies I, II and III)

Observation of general movements

Observation and classification of general movements were performed for studies I, II and III. All recordings were performed and classified by the same physiotherapist (LA), who was also aware of the medical history of the infants. The physiotherapist had participated in GM assessment basic and advanced training courses and had four years of clinical experience in using GM assessment when the classifications were carried out. He was certified by the General Movement Trust (GMT) performing the Prechtl methodology. In order to test inter-rater reliability in study I, a GM assessment trained physiotherapist (GKØ) from a different hospital, who was unaware of both the medical history of the infants and the initial GM assessment classification, performed a second GM assessment classification of the same recordings. This observer had also participated in basic and advanced training courses, had

certification from the General Movement Trust and several years of clinical experience using the Prechtl methodology. Both observers took care not to observe videos for more than 45 minutes without a break, and ensured that a normal example of GMs was observed regulary for calibration.

Classification of general movements

Fidgety movements were defined according to Prechtl as circular movements of small amplitude, moderate speed, and variable acceleration of neck, trunk and limbs in all directions (Prechtl et al., 1997). Normal fidgety movements are characterized as a continuous stream of tiny and elegant movements (Hadders-Algra, 1996) and were classified as normal when they were present (F+, isolated events, or F++, continuous). The sub-classification of fidgety movements with respect to F+ and F++ was not emphasized and not used in the final analysis in the studies. Fidgety movements were classified as abnormal if they were absent (F-) or abnormal in nature; looked like normal fidgety movements but their amplitude, speed and jerkiness were moderately or greatly exaggerated (Fa) (Prechtl et al., 1997).

ENIGMA - Enhanced interactive general movement assessment (study II)

For the development of a method for quantitative evaluation of fidgety movements and prediction of CP it might be a promising path to model different movement patterns recognized by a GM expert. We believed that the best way of interfacing with an expert who analyses visual patterns, was to find ways to represent the modelled knowledge visually. Hence, we developed an interactive data visualization tool called Enhanced interactive general movement assessment (ENIGMA).

Kinematic measurement

Figure 7 illustrates the data acquisition set-up. Kinematic data were acquired at 25 Hz by means of six MiniBird magnetic sensors (Ascension Technology Corporation, Burlington, VT, USA). Six sensors were attached to the infant's forearms, lower legs, forehead and sternum, respectively. The kinematic data comprised the sensors' positions, in terms of x-, y-, z- coordinates relative to a room-fixed coordinate frame, as functions of time. The recordings were edited by the GM assessment certified clinician (LA) simultaneously with the motion data in accordance with the GM assessment methodology. For pre-processing, the set of 18 raw coordinate time series from the 6 sensors was reduced to two dimensions using Principal Component Analysis (PCA). The final PCA data matrix was calculated for each recording

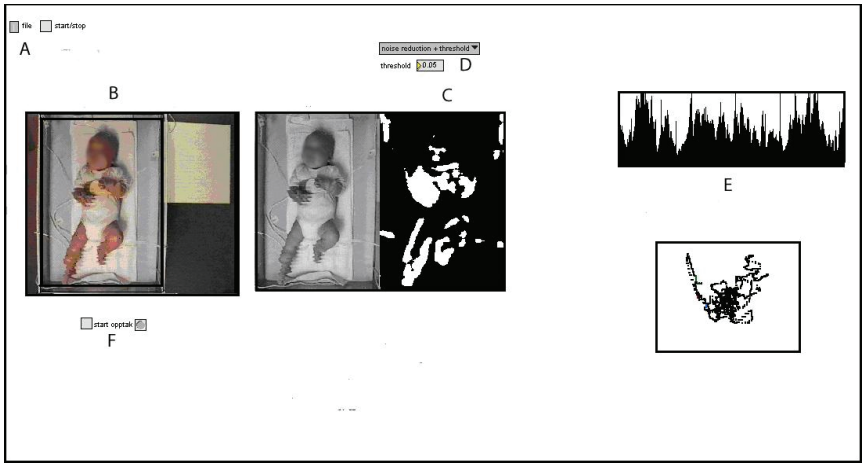

Figure 9: The graphical user interface of the General Movement Toolbox.

Pre-processing (Figure 9-B)

All video recordings were cropped so that only a window containing the mattress with the infant was left for further analysis. This was performed by clicking and dragging a rectangle to the desired area of the mattress in the preview window.

Motion image (Figure 9-C)

The motion image is automatically calculated by the software. A video file typically contains 25 frames per second and one frame contains a number of pixels (M x N pixels) in rows and columns. For many of the video files in this study M = 320 and N = 240 pixels. Each pixel has a value between 0-255 (8 bits) that represents its intensity. The motion image is calculated as the differences in pixel values between subsequent video frames (Jensenius, 2006). When there is no difference from one frame to the next frame, this is displayed as a black pixel in the motion image. When there is a change in pixel values between two frames, this is displayed as a white pixel in the motion image. Hence, the white areas in the motion image represent the movement in the video. A model of the calculation of a motion image is presented in Figure 10.

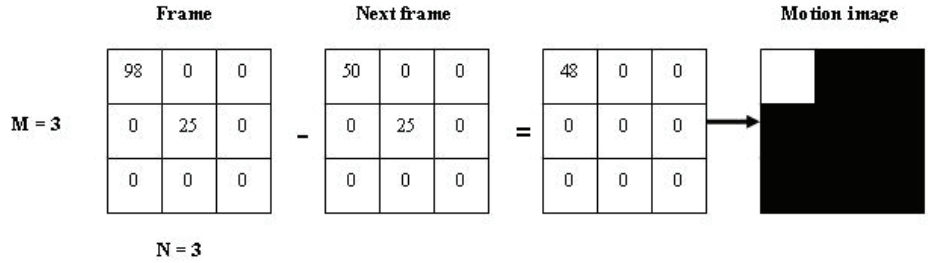

Figure 10: A model of the calculation of the motion image. Each square represent one pixel and the number of pixels is set to 3 x 3 in the model. The difference between frames is calculated in the motion image and displayed in white when there is a change and in black when there is no change.

Filtering the motion image (Figure 9-D)

Depending on the quality of the original video, the motion image must be filtered before further analyses are performed. Two different filtering techniques are normally used; spatial noise reduction (Figure 11) and simple low pass filter (Figure 12). In study III, two different filtering techniques were tested on 20 video recordings containing both normal and abnormal qualities of GMs: a) a simple low pass filter where all pixels below a fixed threshold were removed, and b) the same low pass filter as in a) applied after a spatial noise reduction where single or clusters of pixels falling below a certain size were removed. Figure 13 illustrates the use of the filtering techniques.

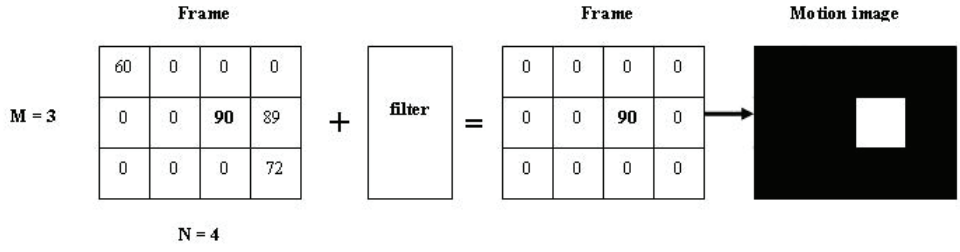

Figure 11: A model of 3 x 4 pixels: spatial noise reduction where single pixels and pixels in clusters below a certain value are filtered (here below 90) .

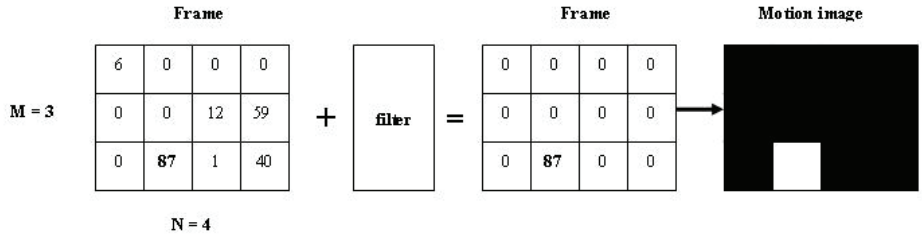

Figure 12: A model of 3 x 4 pixels: low pass filter where all pixels below a certain value are filtered (here below 87).

By testing the different filter techniques a) and b) in video recordings with normal and abnormal GM quality, method b) was chosen after visual inspection of the prepared 20 videos by a GM expert observer (LA). The threshold level was set to 0.05 for all recordings used in study III and study IV (Figure 13). The threshold was chosen to give the optimal combination of maximum visible movement and low noise details occurring from patterns in clothing and the wires attached to the extremities. The final motion image provided the data for further qualitative and quantitative analyses.

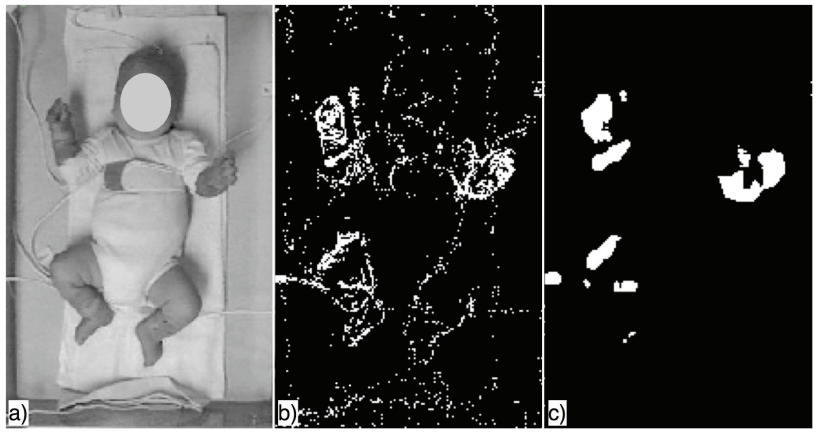

Figure 13: Illustration of the difference as a result of adding the spatial noise reduction filter after low pass filtering of the motion image. From left: a) cropped input image, b) motion image with low pass filter threshold 0.05, and c) motion image with the addition of the spatial noise reduction filter before low pass filter with threshold 0.05. C) was used in our studies.

Visual displays for visual inspection (Figure 9-E)

The General Movement Toolbox has the possibility to display different features derived from the motion image for visual inspection. Jensenius and co-workers had earlier used displays of *Quantity of motion (Q)* (upper part in Figure 9), *Centroid of motion (C)* (lower part in Figure 9) and *Motiongrams* in studies using the Musical Gesture Toolbox (Jensenius et al., 2005, Jensenius, 2006, Jensenius, 2009). These displays were included in the General Movement Toolbox for study III.

Calculation and export of quantitative features (Figure 9-F)

The General Movement Toolbox provides quantitative output data derived from the motion image. These data were saved as an ASCII file fore studies III and IV and were further analysed in the SPSS.

Outcome variables

Quantity of motion (Q)

The feature Quantity of motion (Q) is defined and calculated as the sum of all active (white areas indicating movement) pixels in the motion image divided by the total number of pixels in the motion image. This gives values ranging between 0 and 1, where 1 means that all pixels changed between the two frames. Quantity of motion can therefore be used as an estimate of the amount of movement from a video sequence. By plotting the values over time, a display of Quantity of motion is created (Figure 9, upper right corner) and can be used for visual inspection. In study III, displays in two infants with present and absent fidgety movements were studied in detail, looking for patterns distinguishing the two. In the quantification of Quantity of motion, the mean values (Q_{mean}), maximum values (Q_{max}) and standard deviation (Q_{SD}) were calculated for each recording.

Centroid of motion (C)

The Centroid of motion (C) is calculated as the spatial centre of the active pixels (indicating movement) in the motion image, and may be seen as a correlate to the centre point of the movements of the infant. If this point is plotted over time, a "track" will be displayed as shown in Figure 9 (lower right corner) and can be used for visual inspection. In study III, displays in the same two infants with present and absent fidgety movements as described in Quantity of motion were studied in detail. In the quantification of Centroid of motion, the mean values in the x- and y- direction were calculated (CX_{mean}, CY_{mean}). The variability of the

Centroid of motion was quantified as the standard deviation of the centroid (C_{SD}). The velocity and acceleration of the Centroid of motion were also calculated. The variability of these gives two further quantities: the Velocity standard deviation (V_{SD}) and the Acceleration standard deviation (A_{SD}).

An additional quantitative variable, CP Predictor, was calculated from the combination of three variables by the use of logistic regression; the Centroid of motion standard deviation, the Quantity of motion mean and the Quantity of motion standard deviation. This CP Predictor variable was used in study IV. The combination of Quantity of motion standard deviation and the Velocity standard deviation was also used for prediction of function in children with CP.

Motiongram

A motiongram is a representation of the motion image. Each motion image is averaged to a one pixel wide or tall matrix being plotted over time and displayed (Jensenius, 2006, Jensenius, 2009). Figure 14 shows a model of the creation of a motiongram. This results in either a horizontal or vertical motiongram display. A horizontal motiongram shows the vertical movements in the motion image and vice versa. Although a reduction of the original video, the motiongram gives an indication of how much the infant is moving over time, as well as where in the body the movement is happening (example in Figure 6, page 38). In study III, horizontal motiongrams in two infants with present and absent fidgety movements were studied in detail. The two infants were the same infants used for the study of Quantity of motion and Centroid of motion.

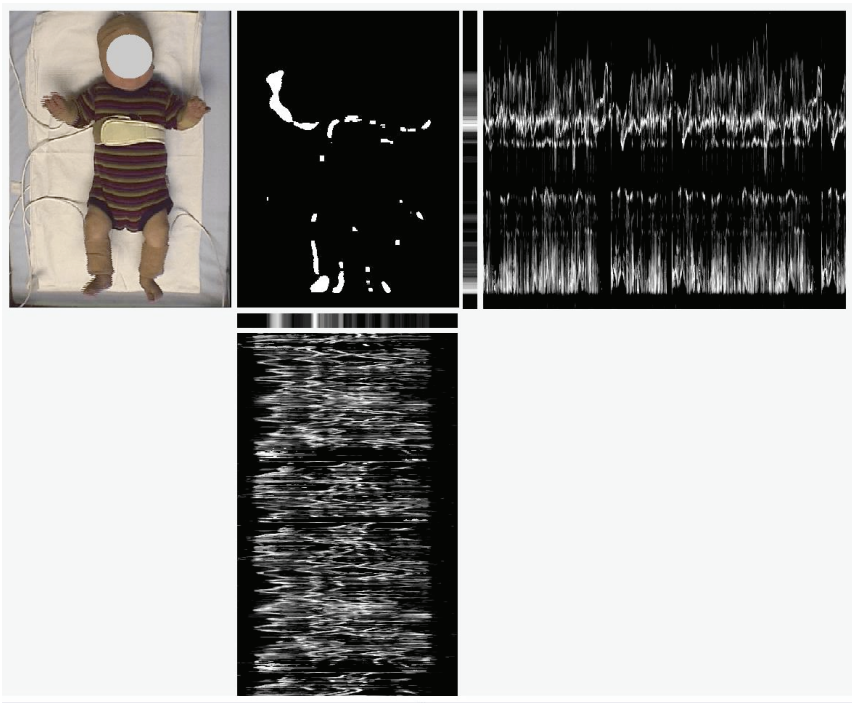

Figure 14: A model of the creation of motiongrams based on the motion image. By averaging the motion image to a one pixel wide and tall matrix, plotting these average pixels over time results in a horizontal and a vertical motiongram that can be used for visual inspection.

Two-year neurological outcome (study I)

All high risk infants enrolled from St. Olavs Hospital (16 of the 25 high-risk infants included in study I) had follow-up in the hospital's outpatient programme for infants at risk of neurological adverse outcome. The child is assessed by a multi-disciplinary team at 3, 9, 15 and 24 months corrected age and at 5 years of age. The team includes a consultant in neonatology, a paediatric physiotherapist, an occupational therapist, a specialist in neuropsychology and a special education therapist. In study I, the same consultant in neonatology (RS) performed clinical neurological examination of all children, and motor and mental skills were assessed using validated tests (AIMS test at 9 and 15 months and Bayley score for motor and mental function at 24 months). Nine children had follow-up at other hospitals in Norway and six of them were followed at institutions with similar structured, multidisciplinary follow-up programmes. Three children had follow-up at a hospital where no structured follow-up programme had been implemented, but where the same, experienced

paediatrician and a child physiotherapist were responsible for follow-up and other subspecialties were involved on clinical indication.

Information regarding CP status for all the low risk infants was obtained from the public health nurse and/or family physician by the use of a questionnaire as none had routine contact with a paediatrician (appendix 2). In order to ascertain that all children with a potential motor problem were identified, all parents were asked to fill in a questionnaire about whether their child had CP or not (appendix 3). Based on the total amount of information, the neurological outcome for each child was classified into three groups by the neonatalogist (RS): cerebral palsy, not cerebral palsy or uncertain (where the answers from questionnaires differed).

Five-year neurological outcome (study IV)

All children participating in study IV underwent a multidisciplinary team examination at 4-7 years of age. Data on the seven children in study IV followed outside St. Olavs Hospital in Trondheim were received from the child's physician and/or physiotherapist. CP was diagnosed according to the European Classification System of cerebral palsy, SCPE (Cans, 2000) by a paediatrician trained in child neurology (KG). The diagnosis was based on all information available from the multidisciplinary team and the physician and /or physiotherapist. We also used the Gross Motor Function Classification System (GMFCS) score for the children with CP. The same trained paediatrician in child neurology at St. Olav University Hospital (KG) scored all children with CP according to the GMFCS and scores were calculated on the basis of information from the child's medical record.

The GMFCS has five levels and determines which of the levels best correspond to the child's abilities and limitations in gross motor function in home, school, and community settings (Palisano et al., 2000). The description for each level is broad and it is not intended to describe all aspects of gross motor function. The classification is based on self-initiated movements, with emphasis on sitting, transfers, and mobility. Distinctions between levels are constructed so that it should be meaningful in daily life. Further, the distinctions are based on functional limitations, the need for hand-held mobility devices (walkers, crutches or canes) or wheeled mobility, and to a lesser extent, quality of movement (Palisano et al., 2000). For each level, descriptions are provided in the following age bands: less than 2 years, 2 to 4 years, 4 to 6 years, and 6 to 12 years. Table 5 shows the general headings for each level in the GMFCS.

Table 5. General headings for each GMFCS level adapted from Palisano (Palisano 1997)

Level I	Walks without Limitations
Level II	Walks with Limitations
Level III	Walks Using a Hand-Held Mobility Device
Level IV	Self-Mobility with Limitations; May Use Powered Mobility
Level V	Transported in a Manual Wheelchair

Statistical analyses

Using a cross sectional design, we assessed to what degree quantitative variables derived from the General Movement Toolbox represented the absence of fidgety movements assessed by the GM assessment (study III). Applying a prospective design, data from the General Movement Toolbox were used to predict how good the method was at diagnosing CP outcome at five years of age (study IV) and how good the GM assessment was at diagnosing CP at two years of age (study I). Based on the samples in study I and IV and the knowledge about true CP status, we calculated the sensitivity and the specificity of the two tests in predicting CP (Altman, 1991).

In study I we wanted to calculate the agreement between the categorical fidgety movement variable (present or absent) performed by observer 1 (LA) and observer 2 (GKØ). The inter-rater agreement could have been presented by per cent agreement but has the weakness that it does not take into account agreement achieved by chance. The measure of agreement between categorical assessments was therefore calculated by Kappa statistics which has the strengths that it considers agreement in excess of the amount of agreement that would be expected by chance (Altman, 1991).

The quantitative variables derived from the motion image using the General Movement Toolbox in studies III and IV gave us the possibility to develop a model to assess to what degree quantitative movement characteristics in infants with absent fidgety movement could detect absent fidgety movements and predict later CP status. Sensitivity and specificity analyses were performed for each quantitative outcome variable and presented as receiver operating characteristic (ROC) curves. In study III the dependent variable was fidgety movements (present or absent) and in study IV it was CP or non CP. Logistic backwise regression models with movement variables derived from the General Movement Toolbox as explanatory variables were used to assess which of the movement variables that had the

highest explanatory power to explain the dependent variable. In accordance to Altman, a backward stepwise regression procedure is useful in deciding a final model to be tested consisting of the most important predictor variable(s) (Altman, 1991).

CHAPTER 8: Summary of papers

Paper I

General movement assessment: Predicting cerebral palsy in clinical practise

The general movement assessment is an observational method used to predict CP in infants at risk of developing neurological dysfunctions. Most of the work on GM assessment has been performed by the same group of researchers. The aim of the present study was to demonstrate the ability of GM assessment to predict CP and evaluate the inter-rater reliability in the classification of fidgety movements.

A prospective study was performed to classify GMs by the use of the Prechtl method in the fidgety movement period to predict later CP. Initial GM classifications were performed by Lars Adde (LA). This observer had the knowledge about the medical history of the infants and had met the parents and observed the infants. An additional blinded GM classification was performed by Gunn Kristin Øberg (GKØ) for inter-rater reliability evaluation. Seventy-four term and preterm infants (135 video recordings) at low and high risk of developing cerebral palsy were included. The absence or presence of CP was reported at 23 months corrected age by the child's physician and the parents.

The results showed that the GM assessment identified all 10 infants that were later classified as having CP. All the infants that did not develop CP were also correctly identified by the GM assessment (LA) except for one infant without CP and with absent fidgety movements. Three infants had uncertain CP status at follow-up. The sensitivity of GM assessment with regard to later CP was 100% with 95% CI (0.73, 1.00) and the specificity was 98% with 95% CI (0.91, 0.99) when the three uncertain cases were excluded. The additional GM assessment classification was performed in 73 of the 74 children. The classification was identical between the two observers in 64 infants (88%) and different in 9 infants. The inter-rater agreement (Cohens Kappa) resulted in *K* value of 0.61 (95% CI (0.37, 0.84)). The results show that the GM assessment used during the fidgety movement period strongly predicts the development of CP. Fidgety movements were classified with 88% agreement between the two observers; the results are in accordance with other studies, and are regarded as having good reproducibility.

Paper II

ENIGMA – Enhanced interactive general movement assessment

Development of a quantitative method for detection of fidgety movements and prediction of CP is dependent on features being effectively elicited from a GM expert. We developed ENIGMA, a software tool for elicitation of fidgety movement knowledge and mathematical feature modelling.

Video and kinematic motion data captured by means of an electronic motion tracking system were collected in 15 recordings containing both normal and abnormal general movements from the fidgety movement period. Video and different visualized features of recorded motion data were shown in synchrony by the developed ENIGMA software. Through an iterative and incremental process between a GM expert and a feature modelling engineer, fidgety movement patterns were modelled. The process was guided by the GM expert comparing movement patterns observed in the video with corresponding visual patterns observed in visualized features.

Three visualized features were identified for the further exploration of fidgety movements on the basis of expert GM knowledge. Present fidgety movements were found to typically be characterized by periodic patterns observable in the visual displays. ENIGMA demonstrated that visual displays based on kinematic measurements revealed characteristic fidgety movement properties. The study was a first step in a new method development and further research should be performed with respect to quantitative detection of fidgety movements using the features/mathematical models in larger populations.

Paper III

Using computer-based video analysis in the study of fidgety movements

Absence of fidgety movements in high-risk infants is a strong marker for later CP. Fidgety movements can be classified by the GM assessment, based on a Gestalt perception of the infant's movement pattern. More objective movement analysis may be provided by computer vision techniques. The aim of the present study was to explore the feasibility of the computer-based General Movement Toolbox to classify absent and present fidgety movements.

GM assessment was performed on 137 video recordings from the fidgety movement period in 82 term and preterm infants at low and high risk of developing CP. The General Movement

Toolbox was used for the analysis of the same recordings. Visualization of the infant's movements was used for qualitative exploration and quantitative variables were derived from the calculation of change in pixels from one video frame to the next.

Visual representation from the General Movement Toolbox demonstrated characteristic patterns of fidgety movements, especially with respect to the motiongrams. Eight quantitative variables were derived and the variability in displacement of the spatial centre of active pixels in the image showed the highest sensitivity (81.5%) and specificity (70.0%) in detection of absent fidgety movements. With the use of triage thresholds at 90% sensitivity and specificity for fidgety movements, the need for further referral was reduced by 70%. This study shows that video recording from the fidgety movement period can be used for qualitative and quantitative analyses of fidgety movements provided by computer vision techniques like the General Movement Toolbox. The General Movement Toolbox may therefore provide assistance in detecting infant's without fidgety movements and seems to identify important predictors for the further development of a prognostic model for prediction of later CP.

Paper IV

Early prediction of cerebral palsy by computer-based video analysis of general movements: a feasibility study.

Paper III showed that it was possible to detect fidgety movements by the use of quantitative variables derived from video recordings by the use of the General Movement Toolbox. The aim of the present study was to investigate the predictive value of the computer-based General Movement Toolbox for the development of CP in young high risk infants. We also wanted to explore if the derived variables could predict gross motor function level in children diagnosed with CP.

Thirty term and preterm high risk infants were included in a prospective study. All infants had participated in studies I, II and III presented in this thesis. Infants were considered to be at high risk of CP development if they had a gestational age lower than 28 weeks and/or a birth weight below 1000 g at birth, or had specific risk factors as described for study I. Video recordings were performed between 10 and 15 weeks post-term age. One recording from each infant was used in the analysis. Video recordings were edited according to the GM assessment methodology and were put together into sequences lasting from 50 seconds to 5 minutes. Several quantitative variables were derived from the motion image: Quantity of motion (Q)

mean, median and standard deviation, Centroid of motion (C) standard deviation. The velocity and acceleration of the Centroid of motion were also calculated. The variability of these gave two further quantities: the Velocity standard deviation and the Acceleration standard deviation. An additional variable CP Predictor (CPP) was quantified from the combination of three variables; the Centroid of motion standard deviation, the Quantity of motion mean and the Quantity of motion standard deviation. Absence or presence of CP and gross motor function of children with CP using the Gross Motor Function Classification System (GMFCS) was reported at 5 years and 7 months median age.

Variability of the Centroid of motion (centre of movement in the infant) in the video had a sensitivity of 85% and a specificity of 71% in identifying later CP. By combining this with variables reflecting the amount of motion (Quantity of motion mean and standard deviation), specificity was increased to 88%. Nine out of ten children with CP were correctly predicted with regard to ambulatory and non-ambulatory function. This study showed that prediction of CP can be provided in young infants by the General Movement Toolbox. The method seems promising and may serve as an objective and feasible tool for early prediction of CP in high-risk infants. Results are based on a small number of infants and must be verified in larger studies.

CHAPTER 9: Discussion

The main results of the thesis

This thesis has confirmed that GM assessment performed by experienced observers during the fidgety movement period is sensitive and specific for prediction of CP. The classification of fidgety movements by two observers also showed a good inter-rater reliability. Hence, this thesis verifies the important role of absent fidgety movements as a significant marker for CP development and present fidgety movements as a significant marker for non-CP development. The thesis has also revealed that it is possible to visualize fidgety movement characteristics derived from kinematic measurements by use of the ENIGMA software tool, and that visual displays identify infants with present and absent fidgety movements by the use of the functionality offered by the General Movement Toolbox. Finally, the thesis has shown that early, non-intrusive prediction of CP by use of computer-vision-based video analysis comprising analysis of quantitative variables derived from the infants' general movements is possible. The results also indicate that early prediction of gross motor function with regard to ambulatory and non-ambulatory function among children with CP at 5 years of age by computer-vision-based movement analysis is possible.

Strengths and limitations

Subjects

Different movement characteristics from the fidgety movement period were the important data source needed for all four studies in this thesis. As many infants as possible at high risk of CP development were included in addition to inclusion of presumably normal infants in the control group. This resulted in a high prevalence of CP in the study groups; 10 out of 74 children in study I had CP (comprising both high and low risk infants), and 13 out of 30 children in study IV had CP (only high risk infants). In order to develop a new diagnostic tool, it was important to include as many infants as possible with a variety of movement patterns. Inclusion of a mix of high and low risk infants used in our studies is in accordance with other studies (Prechtl et al., 1997, Einspieler et al., 2007) and is a common procedure to evaluate the potential sensitivity and specificity of an early assessment technique (Hadders-Algra et al., 2004, Campbell et al., 2002). The clinically important measure of positive and negative predictive values of the computer-vision-based movement analysis cannot be determined without a prospective study of a representative high-risk population.

General movement assessment

Video recordings were used in our studies and this is in accordance with Precht and Hadders-Algra (Prechtl, 1990, Hadders-Algra, 1996, Einspieler et al., 2004). The GMs are the most frequently occurring and most complex movement pattern from the rich repertoire of spontaneous movement patterns (Einspieler et al., 2004) and we chose to focus on the absent or present fidgety movements during the fidgety movement period as the most important feature for CP prediction. This closely matches findings from other studies (Einspieler et al., 2004, Einspieler and Prechtl, 2005, Hadders-Algra, 2004, Hadders-Algra, 2001). Six studies aimed at predicting CP at 2 years of age by the use of the Prechtl method for fidgety movement assessment have resulted in documented overall sensitivities and specificities of 94 % and 82 to 100 %, respectively. The correct identification of all 10 infants that had CP at 2 years of age in study I is in accordance with these results (Prechtl et al., 1997, Hadders-Algra, 2001, Hadders-Algra, 2004, Einspieler et al., 2004, Einspieler and Prechtl, 2005). Study I also demonstrated that knowledge of the medical history, as in a normal clinical context, did not seem to influence the assessment of fidgety movements in a negative way.

The inter-rater variability in study I showed identical classification in 64 of 73 (88%) infants. The inter-rater agreement resulted in a Cohens Kappa value $K = 0.61$ and seems to be in accordance with results demonstrated in other studies (Fjortoft et al., 2009, Geerdink and Hopkins, 1993, Bos et al., 1997, Bos et al., 1998). Einspieler et al. have reported an agreement of between 89% and 93% on video recordings assessed by 90 observers in 358 infants from 11 studies. In four other studies based on 108 infants assessed by 11 observers, the average Cohen's Kappa was 0.88 (Einspieler et al., 2004). Valentin et al. have evaluated 8019 GM assessments from a final test on 18 General Movement Trust training courses held between 1997 and 2002. After a 4- to 5-day training course the correct discrimination between normal and abnormal GMs was 92% (Valentin et al., 2005). Recently, Fjørtoft et al. confirmed the high inter-rater agreement in the study of fidgety movement classification with high to very high inter-rater reliability of 0.75 to 0.91 Kappa values (Fjortoft et al., 2009). The intra-rater consistency of GM qualities during one recording was 92% in one study, which concluded that individual quality of fidgety movements remains consistent for a young infant at a certain date (Mutlu et al., 2008).

There are difficulties associated with the use and interpretation of Kappa values (Altman, 1991). The Kappa value depends upon the prevalence of the condition under study in the

study group. In study I in this thesis, 54 infants (74%) were classified with present fidgety movements (F+) and 10 infants (13%) were classified with absent fidgety movements (F-) by both observers, and the Kappa value was $K = 0.61$. The same rate of inter-rater agreement, but a higher prevalence of infants classified with absent fidgety movements (F-), would give a higher Kappa value (table 6). This fact makes the interpretation of Kappa difficult with respect to comparison with other studies where the proportion of subjects in the different categories is unknown. Altman describes this shortcoming of the Kappa value, but still underlines that it is undoubtedly the right type of approach to calculating inter-rater agreement. However, he promotes the need for showing the raw data if possible when presenting Kappa values for better comparison (Altman, 1991).

Table 6. Comparisons of two observers' classification of present (F+) and absent (F-) fidgety movements in 73 infants with different prevalences in the two categories. A) Classification from study I, B) example of classification with 50% present and absent fidgety movement cases.

A)

		Observer 1		
		F+	**F-**	**Total**
Observer 2	**F+**	54	3	57
	F-	6	10	16
	Total	60	13	73
Kappa, $K = 0.61$				

B)

		Observer 1		
		F+	**F-**	**Total**
Observer 2	**F+**	32	3	35
	F-	6	32	38
	Total	38	35	73
Kappa, $K = 0.75$				

The General Movement Toolbox and quantitative measurements

To demonstrate good validity, the General Movement Toolbox must provide instrument reliability with minimal measurement errors. In the first place this is assumed provided through several years' development of the Musical Gesture Toolbox by Jensenius et al. (Jensenius et al., 2005, Jensenius, 2009). The General Movement Toolbox was a customized version of the Musical Gesture Toolbox, with small changes in the graphical user interface and removal of some minor software modules. Despite years of previous development, there are some aspects that are important to discuss concerning the quantitative measurements of the young infants based on our video recordings and the General Movement Toolbox.

A potential source of measurement error is the procedure for video cropping which is done manually. All video recordings in our studies were pre-processed by cropping the video image to cover only the mattress with the infant. Due to the clear contrast between the mattress and the background and the rectangular shape of the cropping function tool and the mattress, this was easy to perform precisely for all infants. Nevertheless, differences in the cropped video area will consequently influence the calculation of the variable Quantity of motion, resulting in lower values for a motion image with a large cropped area compared to higher values in a less cropped area. The Quantity of motion will also be influenced by different infant clothing. "Bodies" with colours and pictures or stripe designs will increase contrasts in the image and thereby pixel activity compared to one-coloured bodies. Different lighting conditions will have similar effect, influencing the pixel intensity. So will the size of the infant, resulting in higher Quantity of motion values for large infants compared to small infants. Although potential sources of measurement errors, these factors are considered to be small and random with respect to infants with present or absent fidgety movements.

The Centroid of motion was calculated from the active pixels in the motion image, making it independent of the manual cropping. However, all infants had wires attached to their limbs due to the kinematic measurements, and the movement of the wires could influence the Centroid of motion measurements. The main results were based on the calculation of the standard deviation (variation) of the Centroid of motion, making it independent of the amount of motion in the motion images themselves. All infants had the same wires attached to the body in all video recordings, making it unlikely that this has biased the measurements in relation to differences between groups.

The filter setting of the motion image was chosen to give the optimal combination of maximum visible movement and low noise details occurring from patterns in clothing and the wires attached to the extremities. The same filter setting was used for all analysis performed with the General Movement Toolbox in both study III and IV, and is, therefore, highly consistent across studies. The motion image was calculated automatically by the software without any interference from the user and this eliminates possible measurement errors from the motion image calculation. Systematic motion image measurement errors are also unlikely, with reference to earlier use documented in several publications by Jensenius et al.

The procedure for importing the video file, cropping the video and calculation of the motion image is considered as a limited source of measurement error. Further studies should explore the possibility of making a fixed and standard cropped area for all video recordings and should ensure identical one-coloured clothing for all infants. It is an unanswered question whether other filter settings would have influenced our results, and this should be explored in further studies. The high discriminatory ability suggests that instrument reliability was good; otherwise results would have been worse and not so promising. There will always be a trade off between making measurements with minimal measurement errors as in a laboratory setting, and feasibility of easy clinical use, introducing the possibility of measurement errors. Altogether, we consider the measurements provided by the General Movement Toolbox in this thesis to show robustness, reinforcing the concept of a robust method for clinical use.

We are not the only research group using computer-based methods for the study of general movements. Other studies have previously documented use of computer-based measurements in an attempt to assess quantitative aspects of general movement characteristics. By the use of kinematic measurements and electro magnetic sensor technology, a computer-aided approach for differentiation of normal and abnormal GMs during the writhing period of infant development has recently been reported (Kim et al., 2009). Lower-extremity spontaneous movements in infants were studied by van der Heide and co-workers using video recordings and markers on the lower-extremities (van der Heide et al., 1999), and surface EMG recordings have been used to study developmental changes in muscle co-ordination in GMs (Hadders-Algra et al., 1992). As far as we know, analysis of infants with fidgety movement characteristics by use of computer-vision-based technology has not been presented elsewhere.

As demonstrated in study III, the variability of the Centroid of motion (C_{SD}) had the strongest association with the absence of fidgety movements. Larger variability of the Centroid of motion values in infants with absent fidgety movements may suggest a less stable movement pattern where the Centroid of motion position changes more over time. The correlation between the variability of the Centroid of motion and absent and present fidgety movements indicates good construct validity in study III. However, fidgety movements are described as superimposed to concurrent movements, and general movements are defined as one evident movement pattern appearing from a rich repertoire of spontaneous movement patterns (Einspieler et al., 2004). Therefore, it cannot be definitively concluded whether the General Movement Toolbox measures fidgety movements themselves or infants with fidgety movements, implying the measurement of other concurrent spontaneous movements. There might also be other relevant variables which have been overlooked, which are still unexplored with respect to detection of absent fidgety movements, for example in the frequency domain, and further research should reveal such possibilities. Nevertheless, on the basis of our results it seems reasonable to conclude that the General Movement Toolbox provides measurements that substantiate important movement quantities existing in the fidgety movement repertoire, making an objective validation of the fidgety movement assessment.

Early prediction of cerebral palsy

The candidate variables used to develop our prognostic models in study IV were selected from the main variables used in study III and were assumed to be clinically relevant for prediction of CP. This selection of candidate variables is in accordance with arguments from Royston et al. (Royston et al., 2009). The single variable Centroid of motion standard deviation demonstrates an intriguing property in predicting later CP and capturing movement qualities possibly reflecting absent fidgety movements. This demonstrates good internal validity. In study III, a combination of several variables did not improve the models ability to detect absent fidgety movements. In study IV, however, the combination of the CP Predictor including variability of the Centroid of motion, the variability of the Quantity of motion and the mean values of the Quantity of motion increased the specificity. It is not known if this finding might be due to differences in the study sample or the measurement of concurrent movements other than fidgety movements.

Royston et al. claim that there is no widely agreed approach to building a multivariable prognostic model from a set of candidate predictors (Royston et al., 2009). However, some

standard modelling approaches exist. According to Royston, decisions about selecting clinical relevant predictors, choosing a strategy for selection of predictors for the final model, and selection of a measure of model performance have to be made in the process of developing a multivariable discriminative/prognostic model (Royston et al., 2009). In all studies, we assumed that the available movement data were sufficiently accurate for discrimination and prognosis and that they adequately represented the population of interest. We further chose the backward elimination approach by logistic regression as a strategy for selection of final variables, which is in accordance with Roystone et al. (Royston et al., 2009). With respect to assessment of a logistic regression model performance, we used sensitivity, specificity and the area under the receiver operating curve, which is a common statistical approach for such analyses (Altman, 1991). The ROC method is considered the most useful when comparing two or more competing methods or different models like ours.

Due to the consideration of the long term outlook for saved neonates and the fact that early diagnosis of CP is complex, difficult and long lasting, there is acknowledged a need for early identification of infants that will develop CP. Clinical neuromotor assessment instruments available for prediction of CP is few, and study IV offers a novel prognostic model created to foreseeing or predicting future CP. The prediction of future conditions is helpful to guide doctors, physiotherapists and patients in making decisions on further treatment, to select relevant patients for therapeutic research, and to compare differences in performance between hospitals (Moons et al., 2009b). Prognostic models are developed to be applied with new patients. New patients are often referred to as different from but at the same time similar to the patients used to develop the models (Moons et al., 2009a). Altman et al. states that unvalidated models should not be used in clinical practice (Altman et al., 2009). He argues that to obtain the most stringent form of validation, so-called external validation, different patients from those used to develop the model should be used, preferably patients in other centres. Therefore, the model developed in our studies predicting CP in infants needs external validation before it can be considered for ordinary clinical use. An external validation study has just been started at three hospitals in Norway and will continue for the next years to achieve the external validation needed.

Future perspectives for research

Future perspectives for research should comprise validation of the developed prognostic model, improvement of the model's performance and translational research to make the assessment instrument feasible for clinical use.

First, a new instrument, prognostic model or method should demonstrate high validity before it is applied in clinical practice (Moons et al., 2009a). A prerequisite for validity is good reliability. We have demonstrated good instrument reliability, convergent validity, and high predictive validity comprising internal validity. Future perspectives for research should therefore involve assessment of test-retest reliability, divergent validity, and external validity by use in new populations.

Secondly, further development based on results of coming studies and evaluation of new models should be performed to optimize the assessment instrument. Threshold settings, lighting conditions, camera position, and video quality should also be explored for the impact on the model's performance and robustness.

Third, a standard data acquisition set-up for video recordings was used in our studies. Hence, the robustness with respect to requirements for video recordings should be explored in future studies, and the usability of a clinical device should be evaluated.

Finally, Moons et al. argue that the consecutive stages required to produce a clinically usable prognostic model involve developmental studies, validation studies and impact studies. The main focus in this thesis has been the development of the models and internal validation. An impact study quantifies whether use of a prognostic model or instrument improves decision making and patient outcome. For models with high accuracy from several validation studies, this last stage might not be necessary (Moons et al., 2009a).

Clinical implications

Diagnoses of cerebral palsy can open doors to extra resources in schools and in the community and enable early intervention when brain plasticity is high. But the complexity of symptoms, differences in definitions and heterogeneity of function among affected children, make the detection of children with CP at an early age complex and difficult.

This thesis reveals that the GM assessment used during the fidgety movement period strongly predicts CP outcome when used by trained observers. The inter-rater agreement in assessment of fidgety movements is good. This verifies the GM assessment used during the fidgety movement period as a reliable and highly clinical relevant tool for early prediction of CP. The finding might encourage more clinicians to join GM courses and facilitate the use of the GM assessment. However, the GM observer still needs experience, time and observational expertise to ensure a valid judgement. What is necessary experience and sufficient observation expertise is still an unanswered question. This dilemma will always be present for clinicians with limited knowledge about the GM assessment, working alone under time pressure in ordinary clinical settings.

The clinical implications related to the development of our computer-vision-based model for the detection of absent fidgety movements and prediction of CP might become highly significant in near future. There is a considerable need for early neuromotor assessment tools that are objective, clinically available, cheap, and non-intrusive, without needing a high level of expertise for interpretation and analysis. The General Movement Toolbox might provide precisely the assessment instrument needed, helping health professionals to make decisions using objective estimates of the probability of future CP based on early movement analysis as a supplement to other relevant clinical information and test results. The identified movement characteristics relevant for prediction might also improve our understanding of some of the determinants of the course and outcome of children with CP. The identified movement characteristics also supply important objective validation on fidgety movement classification and GM assessment.

The computer-vision-based method appears with internal validity and the good predictive ability might enforce clinical use. The motiongram display intuitively reflects important information about the movements in infants with fidgety characteristics and might become clinically useful in communicating fidgety movement qualities in an understandable way for non-experts. External validation is needed and the developed General Movement Toolbox should evolve through a combination of clinical studies and further method development.

Without doubt, the immediate scientific and methodological implication is the facilitating role these studies will have on further research within the field of computer vision techniques and analysis of general movements by the use of video recordings.

CHAPTER 10: Conclusion

The Prechtl method for the qualitative assessment of fidgety movements between 10 and 18 weeks post term age demonstrated high sensitivity and specificity in the early prediction of CP. The inter-rater reliability in the assessment of fidgety movements was good. These findings verifies the GM assessment used during the fidgety movement period as a good prognostic tool for CP. However, the GM assessment is for users with high expert knowledge and experience.

Using visual displays for observation of absent or present fidgety movements based on kinematic measurements revealed important knowledge about periodic movement patterns by the use of the ENIGMA software. The use of a computer-vision-based tool, the General Movement Toolbox, demonstrated high concurrent validity with GM assessment during the fidgety movement period. Both observation of visual displays like motiongrams and the model based on quantitative variables derived from the video, detected absent and present fidgety movements in high and low risk infants with high sensitivity and specificity. The General Movement Toolbox proved to be feasible for both qualitative and quantitative fidgety movement analysis based on video recordings.

Identified quantitative predictors among infants with absent fidgety movements were used in the development of prognostic models for prediction of CP and ambulatory and non-ambulatory functions among children with CP. The prognostic model based on the variation of the Centroid of motion (spatial centre in the motion image) demonstrated high sensitivity and specificity and the model developed with a combination of predictors correctly predicted 9 of 10 children with CP with reference to the ambulatory or non-ambulatory function group. Hence, the General Movement Toolbox showed intriguing results in the early prediction of CP and ambulatory function among children with CP.

Care must be taken in interpreting the results due to the small study groups. There is a risk that the prognostic model is closely related to the data set and further studies are needed to validate the General Movement Toolbox in new samples of high risk infants. The computer-vision-based motion analysis provides an inexpensive, non-obtrusive solution for the estimation of objective general movement characteristics. Computer-vision-based systems

like the General Movement Toolbox provide simple solutions and break frontiers, using cameras with no instrumentation of the infant.

This thesis provides a novel computer-vision-based method for early prediction of CP in young infants. Quantitative movement variables derived from a single video recording during the fidgety movement period are presented, and results for prediction of CP and ambulatory versus non-ambulatory function in children with CP are promising. The thesis brings insight to a new area, enabling early objective detection of movement hallmarks for later neurological disease. Consequently, this also brings hope for improved research methods in the evaluation of early intervention strategies.

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SPØRRESKJEMA

Barnets navn: _____

Barnets fødselsdato: _____

Dato for siste undersøkelse: _____

1. Kryss av det som passer for din arbeidssituasjon:

☐	☐	☐	☐
Primærlege	helsestasjonslege	barnelege på sykehus	helsesøster

2. Besvar følgende spørsmål med bakgrunn i den kjennskap du har om barnets helsesituasjon og funksjon i dag.

Har barnet cerebral parese?

☐	☐	☐
Ja	Nei	Vet ikke

Kommentar:

3. Er barnet henvist andre instanser for undersøkelse av sin nevrologiske utvikling?

JA ☐ NEI ☐

4. I tilfelle JA, hvilke?

_____

_____

5. Beskriv kort dersom det er andre opplysninger du mener er viktig å ta med som kan ha sammenheng med barnets helse og funksjon i dag:

_____

_____

_____

Appendix 3: Letter and questionnaire sent to parents for collection of neurological outcome at two years of age

Til …….s foresatte.

Studien: ”Spedbarns spontane bevegelser”

Du / dere har tidligere deltatt i studien ”Spedbarns spontane bevegelser”. Formålet med studien var å utvikle en metode for å kunne forutsi fysisk funksjonshemming i form av cerebral parese (CP). Vi ønsker nå å gjøre en oppfølging av denne studien, og vi er derfor interessert i hvordan det går med barnet ditt / deres. Denne henvendelsen går til *alle* som deltok i studien og betyr *ikke* at det er nye funn som tyder på at status eller tilstand til ditt / deres barn er endret.

Vi ønsker nå informasjon om barnets utvikling, særlig med tanke på motoriske ferdigheter. Vi ber derfor om tillatelse til å innhente slike opplysninger fra barnets lege og / eller helsesøster. I tillegg ber vi dere fylle ut vedlagte spørreskjema. Dersom dere samtykker i deltakelse, vil barnets lege/helsesøster bli bedt om å svare på et skjema som er tilnærmet lik det skjemaet som er vedlagt til dere. I skjemaet til lege / helsesøster spør vi i tillegg om barnet er henvist til andre instanser for utredning av sine motoriske ferdigheter. Dersom dette er tilfelle ønsker vi å kunne henvende oss til disse instansene for å få samme informasjon som vi ber om hos lege / helsesøster. Hvis dere og / eller lege / helsesøster er usikre på om barnet har CP eller ikke kan det hende vi tar kontakt med dere med tilbud om en ny undersøkelse av barnet.

Formålet med denne oppfølgingsstudien er å se om det er overensstemmelse mellom det vi fant da vi filmet og registrerte barnets bevegelser som nyfødt og barnets tilstand i dag. Vi ønsker derfor å bruke videomateriale, bevegelsesregistreringene, fødsels- og helsedataene fra det forrige prosjektet samt informasjonen om barnets utvikling i dag. Prosjektslutt er satt til 2014 for å kunne sammenlikne innsamlede data med barnas utvikling senere i oppveksten. Vi ber derfor om samtykke til oppbevaring av data i 10 år for slike mulige etterundersøkelser og understreker at dere i så fall vil få ny forespørsel om dette. Dersom vi ikke ber dere om samtykke til andre studier, anonymiseres dataene ved prosjektslutt (etter 2014). Prosjektet er godkjent av Regional komite for medisinsk forskningsetikk, Midt-Norge og er meldt til Personvernombudet for forskning, Norsk samfunnsvitenskapelig datatjeneste AS.

Deltakelse er frivillig, og man må ikke begrunne hvorfor man eventuelt ikke ønsker å delta. Om man deltar eller ikke har ingen betydning for den eventuelle behandling og oppfølging du / ditt barn får hos lege eller fysioterapeut. Den informasjonen vi innhenter om barnet vil bli lagret og behandlet konfidensielt. Undersøkelsen vil bli publisert slik at ingen av barna kan gjenkjennes. Dersom du / dere ønsker å trekke dere fra studien, behøver dere ikke begrunne dette. Dere kan til enhver tid senere be om at opplysningene blir fjernet fra registeret uten begrunnelse. Dersom det på noe tidspunkt er noe ved undersøkelsen du vil vite mer om, kan du ringe spesialist i barnefysioterapi Lars Adde, St. Olavs Hospital i Trondheim på telefon 73 86 66 25 eller 924 55580.

Hvis du / dere vil delta, ber vi deg skrive under nedenfor. Vi ber deg også fylle ut vedlagte spørreskjema og returnere hvert ark separat i hver sin vedlagte konvolutt så snart som mulig, helst i løpet av en uke. Det tredje arket (det andre eksemplaret av forespørselen) kan du / dere beholde selv.

Trondheim, 29.01.2004

Lars Adde, Spesialist i barnefysioterapi, Det Medisinske fakultet, Universitetssykehuset i Trondheim

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SAMTYKKEFORMULAR

Jeg / vi har lest informasjonen om oppfølgingsprosjektet av studien ”Spedbarns spontane bevegelser”. Jeg / vi samtykker i deltakelse i studien og i at informasjon om vårt barns bevegelsesfunksjon i dag kan innhentes fra behandlende lege og / eller helsesøster og eventuelle andre instanser som oppgis av legen. Jeg / vi samtykker også i at informasjonen som innhentes kan anvendes som beskrevet og at den kan oppbevares til eventuelle etterundersøkelser i 10 år (til prosjektslutt i 2014).

JA ☐

NEI ☐

Barnets navn: _____

Barnets fødselsdato: _____

_____ _____

Sted, dato underskrift (foresatte)

SPØRRESKJEMA

Barnets pasientkode: _____

Dato ved utfylling av skjemaet: _____

1. Fyll inn opplysninger om den legen dere har hatt mest kontakt med angående barnet og den helsestasjon dere har brukt. Dersom du / dere bare har brukt helsestasjonen og dennes lege fylles bare ut informasjon om helsestasjonen.

   Legens navn: _____

   Adresse: _____

   _____

   Telefon: _____

   Helsestasjonens navn: _____

   Adresse: _____

   _____

   Telefon: _____

2. Besvar følgende spørsmål med bakgrunn i den kjennskap du / dere selv har om ditt barns utvikling og funksjon i dag.

   Har barnet cerebral parese?

   ☐ Ja ☐ Nei ☐ Vet ikke

   Kommentar:

3. Dersom det ikke er mulig å besvare spørsmålene ovenfor, gi en kort begrunnelse for dette dersom det er mulig:

   _____

   _____

4. Beskriv kort dersom det er andre opplysninger du / dere mener er viktig å ta med som kan ha sammenheng med barnets helse og funksjon i dag:

   _____

   _____

Paper I

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General movement assessment: Predicting cerebral palsy in clinical practise

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Abstract

Objective: The general movement assessment (GMA) method is used to predict cerebral palsy (CP) in infants with high risk of developing neurological dysfunctions. Most of the work on GMA has been performed from the same group of researchers. The aim of this study was to demonstrate to what extent GMA predicted CP in our hands.
Method: A prospective study was performed using the Prechtl classification system for GMA in the fidgety period to predict later cerebral palsy. The study population consisted of 74 term and preterm infants at low and high risk of developing neurological dysfunction. The absence or presence of CP was reported at 23 months median-corrected age by the child's physician and the parents.
Results: The GMA identified all 10 infants that later were classified as having CP. GMA also identified all the infants that did not develop CP except for one infant with abnormal GMA and no CP. Three infants had uncertain CP status at follow-up. The sensitivity of GMA with regard to later CP was 100% with 95% CI (0.73, 1.00) and the specificity was 98% with 95% CI (0.91, 0.99) when the three uncertain cases were excluded.
Conclusion: Our study indicates that the GMA used in a clinical setting strongly predicts the development of CP. The work supports the results of previous studies and contributes to the

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validation of GMA. The qualitative nature of this method may be a problem for inexperienced observers. Larger clinical studies are needed.

1. Introduction

Despite technical advances and improvements in obstetric and neonatal care over the last two decades, the prevalence of cerebral palsy (CP) remains constant [1]. Survival among extremely low birth weight infants with a high risk of CP has increased, whereas improvements in perinatal care may have led to a small, but significant decrease in CP among term infants [2]. The diagnosis of CP is usually not established until late in the first year of life [3], and mild cases may not be diagnosed until the age of four or even later [4]. Early prediction of CP is considered important in directing appropriate intervention programs and in identifying those children in need of close surveillance [5,6].

Clinical evaluation of newborn infants in order to predict later neurological disabilities is difficult. Dubowitz et al. [7], Prechtl [8] and Amiel-Tison and Grenier [9] have described some well-known neonatal neurological assessment tests. All of these tests are based on the assessment of passive and active muscle tone and a number of elicited reflexes and reactions. The ability of each test to predict neurological outcome in preterm and term infants varies in different studies [8,10–12]. In addition to clinical examination, imaging of the newborn brain with cerebral ultrasound (CUL) and magnetic resonance imaging (MRI) has improved the prediction of neurological outcome in high-risk infants [13,14].

Prechtl and co-workers have studied a special type of spontaneous movements in newborns and small infants, the so-called general movements (GM). Unlike reflexes, spontaneous movements are patterns of movements that are not initiated by any obvious external stimuli. Observation of the infant's GM and especially the so-called fidgety movements (FMs) has shown promising scientific results with regard to prediction of later neurological impairment [10,15]. FMs may be seen at 6 to 20 weeks post-term and are normally present at 10–15 weeks post-term [5]. Lack of normal fidgety movements has been shown to predict neurological outcome at 2 years more precisely than standard neurological examination both in high-risk preterm infants and in term infants with hypoxic–ischaemic encephalopathy [16–18]. Inter-observer reliability varies from 78% to 93% [5,19–21].

Although promising, many questions remain regarding the implementation of GMA in standard clinical practise. Most of the studies on GMA have come from a few groups of researchers, and the generalizability of the GMA as a clinical tool has been questioned [3]. The methodology has a qualitative approach, and classifications are made based on subjective judgements. Professional training, background knowledge about the child's medical history and frequency of observations may influence the evaluation of the GMs.

For several years GMA has been used to evaluate infants at risk for neurological impairment at St. Olavs Hospital, Trondheim University Hospital. The method is used in addition to standard neurological examination and other available techniques including cerebral ultrasound and MRI. The aim of this study was to evaluate, in this clinical setting, to which extent GMA performed during the fidgety period, predicted CP.

2. Subjects and methods

2.1. Subjects

The majority of infants enrolled were from St. Olavs Hospital. High-risk infants (term and preterm) and low-risk preterm infants were included from the neonatal intensive care unit, whereas healthy term infants were included from the maternity ward. In addition, nine high-risk infants were included from four other hospitals in Norway. High-risk infants were included based on the medical history and cerebral ultrasound results. Children were classified into the high-risk group if they had one or more well-known perinatal risk factors for neurological impairment (Table 1). Infants with congenital syndromes and malformations that could interfere with their spontaneous movements were excluded from the study. Only infants with GMA performed at 10–18 weeks post-term were included.

Neuroimaging results from the neonatal period were collected on all high-risk infants. All units involved in the study did sequential US scans on extremely low birthweight infants in the neonatal period. The timing and frequency of US examinations was in accordance with the different unit's own protocols. Magnetic resonance imaging and CT were available to all units involved and were done at the attending physician's discretion.

Table 1 Criteria for high-risk classification of pre-term and term babies

Criteria	Preterm[a] (*n*)	Term[a] (*n*)
Perinatal stroke[b]		3
Perinatal asphyxia[c]		5
Intra-/peri-ventricular hemorrhage (IVH/PVH), grade III or IV	7	
Severe hypoglycemia and *E. coli* sepsis	1	
BW <1000 g and/or GA <28 weeks	14	
Bronchopulmonary dysplasia with suppl. O_2 at discharge	2	

[a] Some of the infants had more than one risk factor.
[b] Perinatal stroke: Two patients with arterial stroke and one patient with a haemorrhagic infarct after open-heart surgery.
[c] Perinatal asphyxia: All five needed assisted ventilation after resuscitation for from 10 min to several days. Three had Apgar scores ≤3 at 5 min. Three developed neonatal seizures with HIE grades II–III and one of these had MRI findings consistent with hypoxia/ischemia in the neonatal period. Two had non-specified signs of perinatal stress and HIE grade I.

2.2. Observation of general movements

The GMA using video recordings were performed 10—18 weeks post-term in order to study the absence or presence of normal fidgety movements. Recordings were performed according to the standard method for GM observation [20], at least 30 min after feeding and lasted for several minutes during periods of active wakefulness. The infant was partially dressed (body vest and nappy), lying supine. The temperature in the room was comfortable (24—28 °C) and the infant had enough space to move spontaneously. The recordings were repeated several times (range 1—5) to ensure that the quality of movements (normal or abnormal) could be accurately judged.

Fidgety movements were defined according to Prechtl as circular movements of small amplitude, moderate speed, and variable acceleration of neck, trunk and limbs in all directions [5]. Normal fidgety movements are characterized as a continuous stream of tiny and elegant movements [10] and were classified as normal when they were present (F+, isolated events, or F++, continuous). Fidgety movements were classified as abnormal if they were absent (F—) or abnormal in nature; looked like normal fidgety movements but their amplitude, speed and jerkiness were moderately or greatly exaggerated (Fa) [5]. The video recordings were edited to include representative samples of movements lasting from 30 s to several minutes for each infant.

All recordings were performed and classified by the same physiotherapist (LA), who also had knowledge of the medical history of the infants. The physiotherapist had participated in GMA basic and advanced training courses and had 4 years of clinical experience in using GMA. He was certified by the General Movement Trust (GMT) performing the Prechtl methodology. In order to test inter-observer reliability, a GMA-trained physiotherapist (GKØ) from a different hospital, who was unaware of both the medical history of the infants and the initial GMA classification, performed a second GMA classification of the same recordings. This observer had also participated in basic and advanced training courses and had certification from the GMT and several years of clinical experience using the Prechtl methodology.

2.3. Neurological outcome at 2 years of age

All infants in the high-risk group enrolled from St. Olavs Hospital (16 of the 25 high-risk infants included in the study) had follow-up at the hospital's outpatient program for young children at risk of neurological adverse outcome. A multidisciplinary team assesses the child at 3, 9, 15 and 24 months corrected age and at 5 years of age before starting school. The team includes a consultant in neonatology, a child physiotherapist, an occupational therapist, a specialist in neuropsychology and a special education therapist. The same consultant in neonatology (RS) did clinical neurological examination of all children, and motor and mental skills were assessed using validated tests (AIMS test at 9 and 15 months and Bayley score for motor and mental function at 24 months).

Of the 9 children who had follow-up at other hospitals, 5 were followed at institutions with similar structured, multidisciplinary follow-up programs. Four children had follow-up at a hospital where no structured follow-up program had been implemented, but where the same, experienced paediatrician and a child physiotherapist were responsible for follow-up and other subspecialties were involved on clinical indication. For all the low risk infants, information regarding CP status was obtained from the public health nurse and/or family physician, as none of these children had routine contact with a paediatrician.

In order to ascertain that all children with a potential motor problem were identified, all parents were asked to fill out a questionnaire about whether their child had CP or not. Based on all this information, neurological outcome for each child was classified into three groups: cerebral palsy, not cerebral palsy or uncertain.

2.4. Ethics

All infants included in the present study had participated in a previous study were parents had approved video recordings of spontaneous movements of their child. Before the present study, all parents received a letter asking their informed consent for their child to participate in this follow-up study. When they approved to participate in the study, they also allowed the investigators access to the medical records of their children and to contact their local health professionals. Parents who did not respond were reminded first by telephone and finally by a letter. Physicians and public health nurses were reminded by a telephone call. The study was approved by the Regional Committee for Medical Research Ethics and Norwegian Social Science Data Services.

2.5. Statistical analysis

Outcome data were compared with data collected from the GMA analysis. Statistics were carried out using the program StatXact-5 (5.0.3). A confidence interval of 95% for sensitivity and specificity were calculated.

3. Results

3.1. Study population

Of the 83 letters sent to the parents, 79 were returned. Four families did not give their consent to contact their family physician and/or the public health nurse. The remaining 75 parents approved to participate in the follow-up study. Of the 75 letters sent to the family physicians and the public health nurses, 74 answers were returned. The final study population consisted of these 74 children (33 boys and 41 girls). Forty-two (57%) infants were born preterm (Table 2). In the preterm group, the median gestational age was 30.5 weeks (range 24—36 weeks) and median birth weight was 1367 g (range 540 to 3800 g). None of the infants in the study group were born after 42 weeks. Among preterm infants 40% were classified as high-risk, whereas 25% were classified as high-risk among the term infants (Table 2).

Of the 25 high-risk infants, 7 had major abnormalities on US defined as IVH grade III—IV with or without PVL. One of

Table 2 Term and preterm infants classified in high-risk and low-risk groups ($n=74$)

Gestational age	High-risk	Low-risk	Total
Term ($\geq$37 weeks)	8	24	32
Preterm (<37 weeks)	17	25	42
Total	25	49	74

these also had congenital hydrocephalus and later developed ventriculitis. One infant had MRI changes consistent with hypoxic/ischemic encephalopathy, two infants had arterial infarcts diagnosed on MRI or CT and one infant had a haemorrhagic infarct diagnosed on MRI. Three infants had minor abnormalities on cerebral US defined as IVH grade I–II. Eleven of the infants in the high-risk group were classified with normal US and/or MRI in the neonatal period.

3.2. Quality of general movements

One hundred and thirty-five GM assessments were performed in the fidgety period between 10 and 18 weeks post-term in the 74 infants (range 1 to 5 assessments per infant). Sixteen of seventeen children with assessments between 16 and 18 weeks post-term also had assessments earlier in the fidgety period. The one child with only one late assessment (at 18 weeks post-term) had abnormal GMA and had CP on follow-up. Observer 1 (LA) performed the initial classification on which the calculations of sensitivity and specificity were based. All FMs judged as abnormal by this observer were identified as absent (F–) and none as abnormal in nature (Fa). In the high-risk group, 12 of the 25 infants were classified as F–, whereas only 1 infant of the 49 infants in the low-risk group was classified as F–.

3.3. Neurological outcome

At follow-up, 10 children had CP, 61 had no CP and three had an uncertain CP status (Table 3). Classifications by health professionals were based on medical information from the child's last consultation at a corrected median age of 23 months (range 9–31 months). Median age of children at follow-up based on the parents report was 26 months corrected age (range 9–34 months). The ten children with CP were classified with full consistence between health professionals and the parent's report. Two infants with a follow-up of only 9 months both had definite CP. The shortest follow-up, except from these two, was 13 months. Sixty-one children were classified with no CP both by professional health workers and by the parents. Two of three children with uncertain CP status were classified as uncertain by both health professionals and the parents, whereas one was classified as uncertain by the parents and as not having CP by the paediatrician. For these three children, a telephone call to the paediatrician 6 months later (at 25, 32 and 32 months follow-up, respectively) revealed a normal outcome for one, an uncertain outcome for one and one with CP.

3.4. Prediction of neurological outcome

Of the 61 infants with normal FMs classified by observer 1, 60 did not develop CP (Table 3). One child with normal GMA was classified as having uncertain CP status at follow-up at 25 months corrected age, whereas 6 months later his CP status was changed to no CP according to the attending paediatrician. Among the 13 infants with abnormal GMA, 10 were diagnosed as having CP at follow-up (Table 3). Of the three remaining infants with abnormal GMA, one had no CP and two had an uncertain CP status (6 months later these two were classified as one with CP, one still uncertain). In the high-risk group, 40% of the infants developed CP and none in the low-risk group (Table 4). The 10 infants with CP are described in details in Table 5.

3.5. Inter-observer comparative classification

An additional GMA classification was performed by a physiotherapist from another hospital (observer 2) in 73 of the 74 children. She was unaware of the initial GMA classification and the medical history of the infants. The classification was identical between observer 1 and 2 in 64 infants (87.7%) and different in 9 infants. Four infants were classified as having fidgety movements by observer 1 and having no fidgety movements by observer 2. Three infants were classified with no fidgety movements by observer 1 and as having fidgety movements by observer 2. Two infants classified with FMs that looked abnormal in nature (Fa) by observer 2 were both classified as normal FMs by observer 1. These two had no CP on follow-up. Three out of the remaining seven infants with different GMA classification had uncertain neurological outcome at follow-up. The inter-scorer agreement (Cohens Kappa) resulted in κ value of 0.61 with 95% CI (0.37, 0.84) for the 73 children.

3.6. Sensitivity and specificity

By leaving out the three children with uncertain CP status, the sensitivity and specificity were calculated for 71 out of 74 children with a definite outcome for observer 1 and for 70 out of 73 children for observer 2. For observer 1 the sensitivity was estimated to 1.0 with 95% CI (0.73, 1.00) and specificity to 0.98 with 95% CI (0.91, 0.99) and for observer 2 the sensitivity was estimated to 1.0 with

Table 3 Classification of neurological outcome in relation to fidgety movements ($n=74$)

Quality of fidgety movements	CP	No CP	Uncertain	Total
Abnormal	10	1	2	13
Normal	0	60	1	61

Table 4 Classification of neurological outcome in relation to risk group ($n=74$)

Risk classification	CP	No CP	Uncertain
High-risk	10	12	3
Low-risk	0	49	0
Total	10	61	3

Table 5 Children with CP at follow-up ($n = 10$)

Case	GA (week)	FV (g)	Risk factors	CP type
1	40	3570	Arterial infarct	Right hemiplegia
2	29	920	IVH grade IV, congenital hydrocephalus, ventriculitis	Right hemiplegia
3	41	3456	Perinatal asphyxia (Apgar 1-4-7, HIE grade 2—3, neonatal seizures, assisted ventilation)	Quadriplegia
4	27	565	IVH grade IV	Right hemiplegia
5	41	3790	Perinatal asphyxia (Apgar 0-0-2, HIE grade II, neonatal seizures, assisted ventilation)	Quadriplegia
6	40	3490	Perinatal asphyxia (Apgar 2-3-6, HIE grade II—III, neonatal seizures, assisted ventilation)	Quadriplegia
7	40	3580	Haemorrhagic infarct after open heart surgery	Left hemiplegia
8	24	717	IVH grade IV	Right hemiplegia
9	24	695	IVH grade IV	CP, unspecified
10	34	1740	Severe hypoglycemia and *E. coli* sepsis	Quadriplegia

95% CI (0.72, 1.0) and specificity to 0.92 with 95% CI (0.82, 0.96).

4. Discussion

The analysis of general movements has been described as a sensitive method to predict later neurodevelopmental disorders in infants. Although the method has been in use for more than 10 years, there are still few reports on its application from outside the scientific groups where it was first described. In this study, we wanted to see if GMA used in a clinical setting, could predict later CP. The GMA classification was not compared to other tests for neurodevelopmental prediction, and the physiotherapist performing the GMA classification was aware of the medical history of the infants.

General movement assessment performed during the fidgety period identified all infants that later developed CP. Furthermore, normal FMs correctly identified infants that did not develop CP apart from one child. These results support that GMA is a good method to identify those at risk for developing CP [5,16,22], and that normal FMs in high-risk infants can be used to predict a low risk of developing CP.

In a study, by Prechtl et al. [5], a mixture of high- and low-risk infants was included, similar to the approach in the present study. In that study, fidgety movement assessment predicted CP with a sensitivity of 95% and a specificity of 96%. Regardless of the different etiological factors predisposing for CP, it appears that abnormal FMs is a common phenomenon for infants that later develop CP.

In the present study neurological outcome was assessed at a median corrected age of 23 months. This corresponds well with other studies [16,17]. An experienced paediatrician followed all high-risk infants, and majority of high-risk infants were enrolled in a structured follow-up program for young children at risk of neurodevelopmental adverse outcome. However, the range of age at follow-up was wide (13—31 months median corrected age when two infants with CP classified at 9 months were not taken into account). Milder forms of CP may present later in childhood, leading to an underestimation of CP in this study. Although GMA appears to be a good method to predict CP which presents at an early age, it is still an unanswered question if GMA is equally good in predicting outcome in those with a milder form of CP.

Follow-up in the low-risk group was based on information by health professionals who are not necessarily trained to detect subtle neurological symptoms in very young children. However, the prevalence of CP in the general population is as low as 1.50—3.00 per 1000 live births [4]. The likelihood of any of the 49 children in this group having CP, despite a normal development as judged by a public health nurse/family physician and parents at 26 months of age, is therefore very low.

Three infants had an inconclusive clinical outcome. All these three also had non-concordant GMA classifications by the two observers. Two of the nine infants with non-concordant GMA classifications were classified with abnormal fidgety movements (Fa) by observer 2 and with normal FMs by observer 1. The long-term outcome of infants with fidgety movements that look abnormal in nature (Fa) is less clear and may turn out to be cerebral palsy, developmental retardation or minor neurological dysfunctions [5]. In a 3-year follow-up study of 16 infants with Fa classification, three turned out normal, seven showed evidence of developmental retardation or minor neurological signs and six developed CP [5]. The present study was not designed to detect neurological dysfunctions other than CP. It is, therefore, not possible to know if children who were classified differently by the two observers will develop other "soft" neurological signs at an older age.

Knowing the medical history of the infants may have biased the judgements of the physiotherapist in our study (observer 1). An inter-observer concordance of 87.7% as reported in this study is in accordance with that reported by others [20]. Agreement between observers in almost 90% of cases makes it unlikely that the initial classification was significantly biased.

The most frequent abnormality on neonatal cerebral ultrasound in high-risk infants in this study was the presence of IVH grade III—IV, whereas none were diagnosed with cystic PVL in the absence of IVH. This is most likely due to the way infants were recruited. In order to validate the GMA method with regard to prediction of CP, high-risk infants were recruited if they were considered at high risk of motor impairment based on the presence of major US abnormalities or MRI findings or the clinical history. Intraventricular haemorrhage can be easily detected on early US scans, whereas the detection of cystic PVL may depend on serial US

scans beyond the first 28 days of life [14]. One child with IVH grade I and one child with normal neonatal US scan had MRI findings at 4 years of age consistent with PVL. This suggests that a diagnosis of PVL may have been missed and that infants with PVL were not included in the present study unless they had other major risk factors that made them eligible.

The GMA is non-invasive, cheap and independent of advanced technical equipment. Performing the GMA does not seem to put the child in a stressed situation. The most experienced GM assessors claim that the GMA is easy to learn and easy to perform [5,10]. In most studies published about GMA, the observers have been very experienced. The physiotherapists in this study were also experienced, and it is therefore still an unanswered question how much experience the observer needs to make a valid clinical assessment. The whole procedure, including video recording, editing and classification, takes approximately one hour per assessment. In addition, repeated assessments are often necessary to perform an optimal GMA. An informal telephone interview to some of the larger neonatal intensive care units in Scandinavia, revealed that although the neonatologists and physiotherapists had a fair theoretical knowledge of GMA, very few used it in clinical practise. This indicates that more scientific documentation and validation in clinical trials is needed.

5. Conclusion

Although small, this study indicates that GMA, used in a clinical setting in a high-risk population, can be a useful tool to predict later CP. The study supports the results of previous studies and contributes to the validation of GMA. More studies in larger populations are needed to verify the results, especially in predicting mild CP.

The qualitative nature of this method may be a problem for clinicians working alone, implying a risk of drifting away from the standards of the methodology. An aim for future studies is therefore the development of more objective classification criteria and a standardised way of analysing spontaneous movements.

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Paper II

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ENIGMA – Enhanced interactive general movement assessment

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Abstract

General movement assessment is an accurate clinical method for predicting severe neurological dysfunctions such as cerebral palsy in young infants. Development of a computer-based diagnosis support system based on the General Movement Assessment method is dependent on features being effectively elicited from a General Movement expert. We present ENIGMA, a software tool for General Movement knowledge elicitation and modeling.

Video and motion data were collected in 15 recordings containing both normal and abnormal general movements from the fidgety period of infant development. ENIGMA shows video in synchrony with different visualized features of recorded motion data. Movement patterns are modeled through an iterative and incremental process, where the General Movement expert is guiding the modeling process through comparing movement patterns observed in video with corresponding visual patterns observed in visualized features, and giving feedback to the knowledge engineer.

Three visualized features were developed for exploring the so-called fidgety movements. The interactive work procedure introduced by ENIGMA enabled explicit motion features to be defined based on unconscious expert knowledge. Normal fidgety movements were found to be partly characterized by periodic patterns.

Our results demonstrate that ENIGMA is a capable tool for General Movement expert knowledge elicitation. It facilitates the modeling process and provides a basis for detailed discussions. Clinical and technical concepts are communicated well through visual notions.

Keywords: Expert knowledge modeling; Signal visualization; General movements; Visualized features

1. Introduction

Early detection of cerebral palsy (CP) enables health professionals to start therapy early in the infant's development. Several methods for early assessment of neurodevelopmental disorders in infants are available, but their accuracy in predicting CP varies (Hadders-Algra, 2001). General movement assessment (GMA) is a promising neurological assessment tool with regard to early detection of CP (Einspieler, Precthl, Bos, Ferrari, & Cioni, 2004). Based on clinical observation and assessment of general movements (GMs), especially fidgety movements (FMs), this method has obtained very high sensitivity (95%) and specificity (96%) in predicting CP in infants with high risk for neurodevelopmental disorders (Prechtl et al., 1997). FMs are defined as an ongoing stream of small, circular and elegant movements of the neck, trunk, and limbs, and can be observed as early as 6 weeks and as late as 20 weeks post term. The quality of FMs accurately reflects the state of the infant's nervous system (Einspieler et al., 2004; Prechtl et al., 1997). GM observers study infant movement while the infant is in active wakefulness (Prechtl, 1974). Movements are recorded on video for subsequent offline assessment (Einspieler et al., 2004). A GM observer will characterize the movements in the fidgety period as one

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out of four FM types: F−, Fa, F+ or F++. Here, F− and Fa represent abnormal GMs, while F+ and F++ represent normal movements (Einspieler et al., 2004). Normal FMs are usually correlated with healthy development, while the absence of FMs implies a high risk for CP. However, GMA is a subjective procedure based on the observer's acquired expertise. Although seemingly effective, GMA is not necessarily easily applicable in a clinical setting, possibly due to its subjective character (Adde, Rygg, Lossius, Øberg, & Støen, 2006), and there is an incipient demand for more objective methods (Conover, 2003; Meinecke, Breitbach-Faller, Bartz, Rau, & Disselhorst-Klug, 2003).

Expert systems are designed to capture the knowledge of domain experts, store the experts' knowledge in computer format, and subsequently perform the task of the experts. The activity of gathering expert knowledge for expert systems is called knowledge acquisition (KA). KA is often considered a difficult problem and a bottleneck in development of expert systems (Feigenbaum & McCorduck, 1984). While KA encompasses information retrieval from all knowledge sources, knowledge elicitation (KE) techniques focus on extracting knowledge directly from experts. KE techniques commonly discussed in the literature include unstructured interviewing (Cullen & Bryman, 1988; Hoffman, 1987), protocol analysis (Cullen & Bryman, 1988; Hart, 1985; Newell & Simon, 1972), repertory grids (Boose, 1989), prototyping (Grabowski et al., 1988; Waterman, 1986), multidimensional scaling (Elliot, 1986), cluster analysis (Cooke et al., 1987), event recall (Hoffman, 1987), discourse analysis (Belkin, Brooks, & Daniels, 1987) and card sorting (Burton, Shadbolt, Hedgecock, & Rugg, 1987). In recent years, the knowledge elicitation process has commonly been referred to as a modeling effort.

As part of an effort to quantitatively evaluate GMs, and especially FMs, modeling different movement patterns recognized by GM observers seems to be a promising path, considering the reported performance of skilled GMA experts (Prechtl et al., 1997). GM knowledge elicitation is a complex task, because clinical experience largely is *unconscious knowledge* (Mitta, 1989), which is hard for a GM observer to express explicitly. Many movement assessment skills are taught and learned by examples and can only be properly explained by examples.

We believe the best way of interfacing with an expert that analyzes visual patterns, is to find ways to represent the modeled knowledge visually. We have solved the knowledge modeling problem for our specific problem domain by developing an interactive data visualization tool called ENIGMA (Enhanced Interactive General Movement Assessment). The software makes it possible to interactively compare movement patterns observed on video with corresponding patterns in recorded signals. ENIGMA shows infant video in synchrony with different visualized features (Vitures) of movement data. A viture is similar to a *feature;* it comprises methods for data processing, but additionally, it includes a corresponding visualization method. The goal of a viture is to process raw data and visualize the result such that investigated movement patterns are well represented. Thus, ENIGMA helps GM observers and knowledge engineers communicate clinical and technical concepts through visual examples. A viture can be seen as a mediating representation (Angele, Fensel, Landes, & Studer, 1998). We focus here on ENIGMA as a support tool for iterative and incremental GM expert knowledge elicitation and modeling, and investigate whether it is possible to model objective features from fidgety movements based on GM expert elicitation using ENIGMA.

2. Materials

In a recent study, Adde et al. (2006) collected and GM assessed video recordings of 74 infants. The study was designed to include patients from different birth weight and gestational age groups, and all infants have been clinically confirmed as having CP or not at a 2-years' follow-up.

Although not reported in Adde et al., motion data in terms of *x*-, *y*-, and *z* coordinates was captured simultaneously with each video recording at 25 Hz using six miniBird motion sensors (Ascension Technology Corp., Burlington, VT, USA). One sensor was placed on each of the infant's wrists, one on each ankle, one on the sternum and one on the forehead. The length of the recordings ranged from 5 to 15 min.

In the present study we used video and motion data from a selected subset of the data of Adde et al. A certified GM observer carefully selected recordings found suitable for use with ENIGMA, ensuring a representative broad span of different movement patterns available for observation. The subset consisted of 15 recordings based on 14 patients, five of which were labeled F+, two were labeled F++, one was labeled Fa, and seven were labeled F−. Informed consent was given from parents of all patients prior to recording.

3. ENIGMA

3.1. Architecture and implementation

ENIGMA was implemented using Java and MATLAB (system architecture is shown in Fig. 1). Functionality from the Java Media Framework (JMF) was used for playback of video. A component-based architecture and MATLAB's powerful plot functionality combined with extensive libraries for scientific prototyping, ensures that vitures can be added easily.

As shown in Fig. 2, the main program code written in Matlab uses the Java *VideoPlayer* component for video display. The VideoPlayer itself has built-in controls for playing, pausing and stopping, and also a slider to scroll back and forth in the video. Video recordings were captured to AVI format for use with the VideoPlayer. The number of seconds of each viture to display on the screen at any time

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Paper III

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Using computer-based video analysis in the study of fidgety movements

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ABSTRACT

Objective: Absence of fidgety movements (FM) in high-risk infants is a strong marker for later cerebral palsy (CP). FMs can be classified by the General Movement Assessment (GMA), based on Gestalt perception of the infant's movement pattern. More objective movement analysis may be provided by computer-based technology. The aim of this study was to explore the feasibility of a computer-based video analysis of infants' spontaneous movements in classifying non-fidgety versus fidgety movements.
Method: GMA was performed from video material of the fidgety period in 82 term and preterm infants at low and high risks of developing CP. The same videos were analysed using the developed software called General Movement Toolbox (GMT) with visualisation of the infant's movements for qualitative analyses. Variables derived from the calculation of displacement of pixels from one video frame to the next were used for quantitative analyses.
Results: Visual representations from GMT showed easily recognisable patterns of FMs. Of the eight quantitative variables derived, the variability in displacement of a spatial centre of active pixels in the image had the highest sensitivity (81.5) and specificity (70.0) in classifying FMs. By setting triage thresholds at 90% sensitivity and specificity for FM, the need for further referral was reduced by 70%.
Conclusion: Video recordings can be used for qualitative and quantitative analyses of FMs provided by GMT. GMT is easy to implement in clinical practice, and may provide assistance in detecting infants without FMs.

1. Introduction

Preterm infants are at increased risk for adverse neurodevelopmental outcomes [1]. Up to 18% of surviving infants who are born extremely preterm develop cerebral palsy (CP) [2], and the total rate of neurological impairments is up to 45% [3–5]. Neuroimaging and clinical neurological examination during the neonatal period are used to assess the risk of later disabilities. Follow-up programs after discharge are implemented in most tertiary care centres caring for these infants in order to provide specific intervention programs and accurate information to parents about their infant's capabilities and prognosis.

A new approach to functionally assess the young nervous system has been presented by Prechtl [6–8]. Assessment of general movements (GMs), a part of the spontaneous movement repertoire, is a reliable and sensitive tool for the assessment of infant motor development [9,10]. In particular, the absence of the so-called fidgety movements (FMs) in infants at 9–20 weeks post-term age has been shown to be a marker for later disability and cerebral palsy in particular [7,11–13].

FMs are small movements of moderate speed with variable acceleration of neck, trunk, and limbs in all directions [7,14]. The quality of GMs is observed from video recordings and evaluated by trained observers, and the assessment of general movements is based on a global visual Gestalt perception described by Konrad Lorenz [15]. Lorenz described the mechanism of Gestalt perception as analogous to "subconscious conclusions", or as three classical steps of inductive natural science; accumulation of observations, systematic ordering of these observations and abstraction of a governing principle. Lorenz highlighted the danger of attending details and loosing the Gestalt perception that is sought [15]. It is, therefore, crucial that the general movement assessment (GMA) observer masters the principle of not focusing on any details in the infant movements during the assessment.

Due to the experience that is needed and the qualitative nature of GMA, the implementation, generalizability and overall utility of the method have been questioned [11,16,17]. There are indications that

Abbreviations: GM, general movement; FM, fidgety movement; GMA, general movement assessment; GMT, general movement toolbox.

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GMA is limited in use in ordinary clinical practice [18]. The Gestalt perception technique requires experience, and clinicians working alone will be at risk of drifting away from the GMA standards over time. Verification of a GMA result needs a second opinion from another experienced GMA observer. Computer-based analysis of GMs, and the incorporation of its results in clinical follow-up programs may offer a supplement to existing clinical methods.

New motion capture technologies have made it possible to perform quantitative analyses of movement and, thereby, discrimination of normal versus pathological movement based on objective criteria. However, such methods are often restricted to laboratories because of the need for comprehensive instrumentation and advanced analyses [19–22]. To be the first choice in clinical practice, computer-based analysis should be quick to set up, easy to use, and noninvasive for the subjects being studied. Recently, by the use of 2D video recordings, Jensenius et al. [23] developed the Musical Gesture Toolbox (MGT), a software collection for performing video analysis of music-related movements in musicians and dancers. In addition to extracting quantitative measures from the movement in the video recording, the MGT also visualises the qualities of movement. One visualisation method is the *motiongram*, a 2D representation of movement over time [24]. For this study we have developed the General Movement Toolbox (GMT) as a software solution for studying general movements in young infants.

The aim of this study is to 1) describe the usability of *motiongrams* in the study of FMs, and 2) by using the GMT and quantitative parameters, to investigate the ability to detect non-fidgety versus FMs.

2. Subjects and methods

2.1. Subjects

The study group was recruited from St. Olav University Hospital, Trondheim, Norway. Most infants had participated in a previous study on GMA [11]. A convenience sample of preterm and term infants at low or high risk of neurological impairment was included during the period from 2002 to 2004. Infants born after 28 weeks of gestation without any pre- or postnatal complications were considered to be at low risk for neurodevelopmental disorders. Infants were considered to be at high risk of neurodevelopmental disorders if they had a gestational age lower than 28 weeks and/or a birth weight below 1000 g at birth, or had specific risk factors as described elsewhere [11]. All infants had at least one video recording of GMs available during the fidgety movements' period. Written consent was obtained from all parents, and The Regional Committee for Medical Research Ethics and Norwegian Social Science Data Services approved the study.

2.2. Video recordings

The number of recordings performed on each infant varied from 1–5, and recordings were performed between 10 and 18 weeks post-term age. As infant movements were also used for 3D electromagnetic sensor measurements, all infants had motion tracking sensors attached to each extremity, on the sternum and on the forehead. Recordings were done with the infant placed in supine position on a standard mattress during active wakefulness, wearing a diaper and a body. Movements were recorded with a stationary digital video camera (Sony DCR-PC100E) placed above the infant. The GMA observer (LA) edited each video recording according to the procedure described by Einspieler [14]. The edited recordings of 3–15 min were the basis for the GMA. In order to optimize the material for analysis using the GMT, all videos were later cut down to 0.5–5 min sequences. In this last editing process, all movements due to sensor wire movements or other disrupting movements in the video image were omitted.

2.3. Quality of general movements

The GMs were classified following the Prechtl's method of GMA [14], and FMs were defined according to the definition of Prechtl [7]. The FMs were classified as normal when they were present (F+ if intermittent, or F++ if continuous), or as abnormal if they were absent (F−) or abnormal in nature (Fa), i.e. if they looked like normal FMs but their amplitude, speed and jerkiness were moderately or greatly exaggerated. Classification of FMs by GMA was further used as the gold standard for the evaluation of the General Movement Toolbox analysis.

2.4. The Musical Gesture Toolbox (MGT)

The Musical Gesture Toolbox has been developed by Jensenius et al. in 2004 and was made available as open source software in 2005 [23]. It was developed for studying various types of music-related movements (e.g. sound-producing, ancillary, and communicative), and contains tools for playing video, making image adjustments, cropping, and carrying out different types of qualitative and quantitative analyses both in real time and non-real time. For quantitative analyses, the MGT outputs numerical data, whereas various visual representations are used for observation and qualitative analyses. For the purpose of studying GM qualities, MGT was customized into the General Movement Toolbox (GMT) by making some changes in the graphical user interface and removing some software modules specially designed for the study of music-related movements.

2.5. The General Movement Toolbox (GMT)

The General Movement Toolbox includes the following parts and functions: 1) playback of pre-recorded video files, 2) pre-processing the video by cropping the image to the desired observable area, 3) calculation of the motion image, 4) filtering the motion image, 5) creation of motiongrams for visual inspection and 6) calculation and export of quantitative features from the motion image. The graphical user interface (GUI) of GMT is shown in Fig. 1. In a typical workflow, the user opens a pre-recorded video file, plays the video using the tools in the upper left corner (Fig. 1), crops the image to the desired area by clicking in the preview window, and selects the appropriate pre-processing settings.

All video recordings in the present study were cropped so that only a window containing the mattress with the infant was left for further analysis (Fig. 1). After cropping, the motion image was created by identifying the change for each pixel between two frames (Fig. 1). In a motion image each pixel represents a point value of 0 and 1, 0 being black and representing no movement, and 1 being white and representing movement. Depending on the quality of the original video, the motion image must be filtered before carrying out further analyses. Two different filtering techniques were tested on 20 video recordings containing both normal and abnormal qualities of GMs: a) simple low pass filter where all pixels below a fixed threshold were removed, and b) the same low pass filter as in a) applied after a spatial noise reduction where single or clusters of pixels falling below a certain size were removed. Method b) was chosen after visual inspection of the prepared videos by a GM expert observer (LA), and the threshold level set at 0.05 for all recordings (Fig. 2). The threshold was chosen to give the optimal combination of maximum visible movement and low noise details occurring from patterns in clothing and the wires attached to the extremities. The final motion image provided the data for further qualitative and quantitative analyses.

2.6. Motiongram

A motiongram can be seen as a representation of the motion image, where each motion image frame is averaged to a one pixel wide

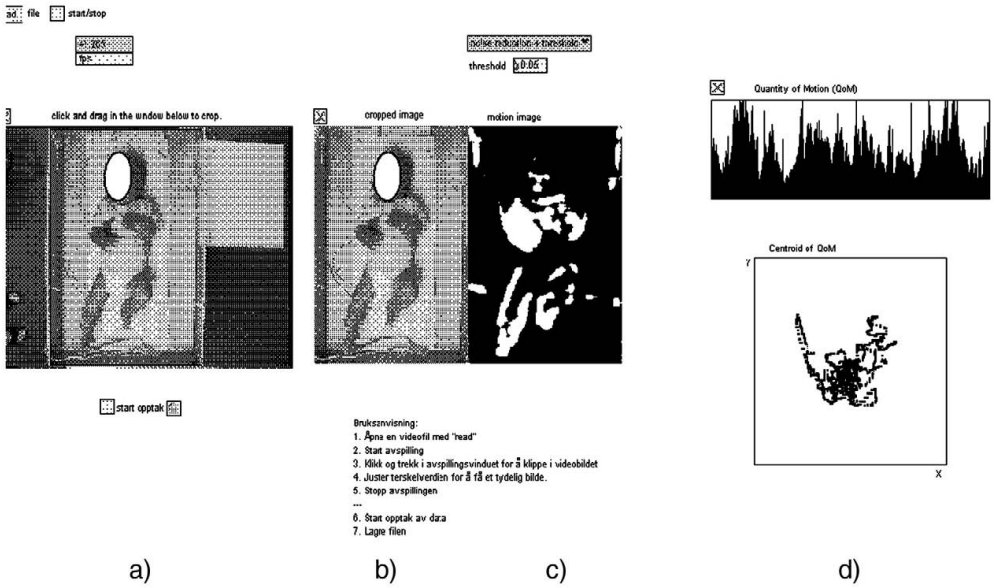

Fig. 1. The GMT graphical user interface: a) input video, b) cropped video and c) motion image. d) The upper section; display of quantity of motion, the lower section; display of the centroid of motion. The tuning and threshold button is above the motion image in the interface and pre-recorded video file is browsed by clicking in the upper left corner of the interface.

or tall matrix being plotted over time. This results in either a horizontal or vertical motiongram display. Fig. 3 shows horizontal motiongrams of one infant with present and one with absent FMs. Movements of upper and lower extremities are seen at the top and the bottom of the image, respectively, and the limited movements of the trunk are seen in the middle part of the motiongram. Although a reduction of the original video, the motiongram gives an indication of how much the infant is moving over time, as well as where in the body the movement is happening.

2.7. Quantitative measures

Quantity of motion is calculated as the sum of all pixels that change between frames in the motion image divided by the total number of pixels in the image. This gives values ranging between 0 and 1, where 1 means that all pixels changed between the two frames, and 0 means that no pixels changed between frames. Quantity of motion can therefore be used as an estimate of movement from a video sequence as shown in Fig. 1. The mean values (Q_{mean}), maximum values (Q_{max})

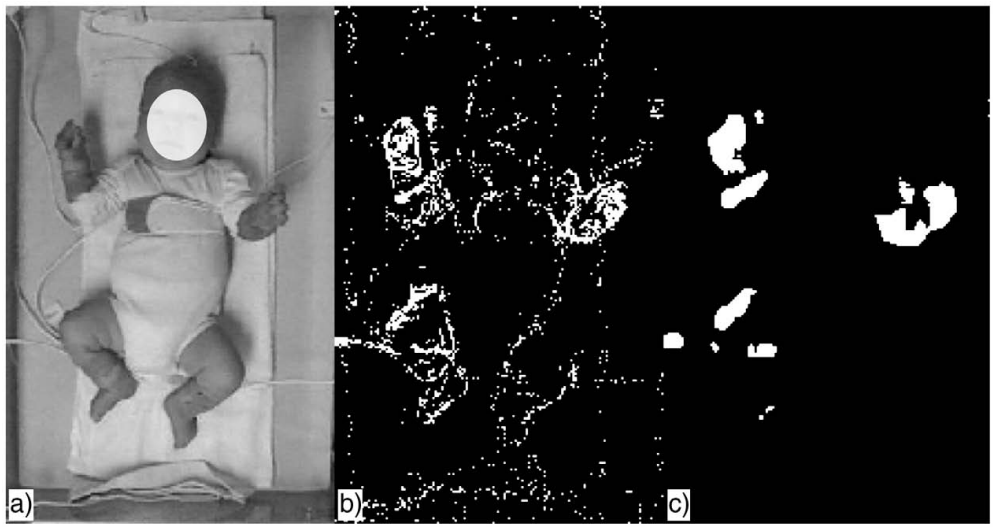

Fig. 2. Illustration of the difference between adding the noise reduction algorithm after low pass filtering the image. From left: a) cropped input image, b) motion image with low pass filter threshold 0.05, and c) motion image with added noise reduction algorithm before low pass filter with threshold 0.05.

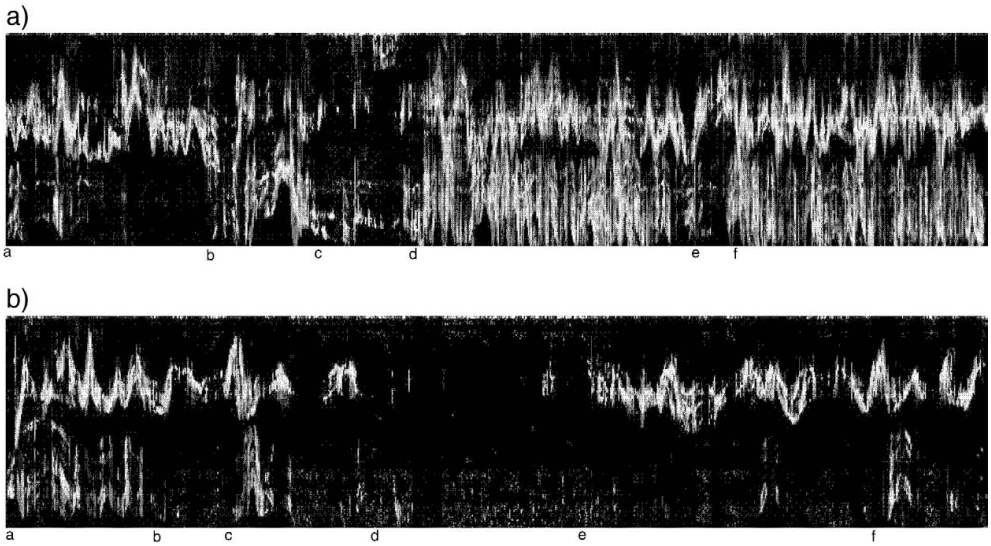

Fig. 3. Examples of displays with motiongrams; a) sequence containing movements for an infant with FMs and b) a movement sequence for an infant with absent FMs. Time running along the *x* axis, and vertical movements on the *y* axis.

and standard deviation (Q_{SD}) were calculated for the quantity of motion for each recording and served as outcome variables. The *centroid of motion* is the spatial centre of the positive pixels in the motion image, and may be seen as a correlate to the centre point of the movements of the infant. Fig. 1 displays how the centroid of motion is changing position during a video sequence. The mean values of centroid of motion in the *x*- and *y*-directions were calculated (Cx_{mean}, Cy_{mean}). The variability of the centroid of motion as a function of time was quantified as the standard deviation given by time averaging. The resulting scalar quantity is the standard deviation of the centroid (C_{SD}). The variability of velocity and acceleration of the centroid of motion were given as time derivates, and the standard deviation of these giving two further quantities; the standard deviation of the velocity (V_{SD}) and the standard deviation of the acceleration (A_{SD}).

2.8. Statistics

Quantitative data were exported as Ascii files using the non-real time mode of GMT. Data were analysed using Matlab version R2008a and SPSS version 15.0. Data were tested for normality distribution using a Kolmogorov–Smirnov test in the group with present FMs, but not in the group with absent FMs due to its small sample size. The estimated group means with standard error for infants with absent and present FMs were calculated. Between-group differences were tested by using independent sample *t*-tests. Sensitivity and specificity analyses were performed for each outcome variable and presented as receiver operating characteristic (ROC) curves. Area under the curve was also calculated as a measure of strength of the model. Logistic-regression models on fidgety versus non-fidgety as dependent variable were performed to investigate the strength of the association between the dependent and each of the independent variables. The association between age at the time of assessment and length of the final video recording on the motion image variables was explored using a Pearson correlation test. By the use of a logistic-regression enter model we assessed whether a combination of motion image variables would give higher sensitivity and specificity than only single variables.

A triage test [25] based on data from the General Movement Toolbox was used as an adjunct to clinical GMA for diagnosis of FMs. We defined a GMT sensitivity (the ability to identify absence of FMs) of 90% and specificity (the ability to identify the presence of FMs) of 90 and 80%. Values classified above the upper threshold were likely to have absent FMs and recordings classified below the lower threshold were likely to have present FMs. Recordings falling between the two thresholds would be recommended for referral for clinical GMA.

3. Results

Eighty-two infants at high ($n=32$) and low ($n=50$) risks for later neurological impairments were included. The study group consisted of 37 boys and 45 girls. Forty-eight infants (58.5%) were born preterm. In the preterm group, the median gestational age was 29.5 weeks (range 23–36) and median birth weight was 1910 g (range 470–3350). A total of 137 video recordings were obtained from the 82 participating infants in the period 10–18 weeks post-term age with a median recording age of 13 weeks. The median length of the video recordings used for quantitative analysis was 3.3 min (range 0.5–5.1). Out of 137 recordings, 27 were classified with absent FMs and 110 with observable FMs by GMA. None of the recordings was classified with FMs that was abnormal in nature.

Two motiongrams from the real time mode of the GMT are shown in Fig. 3a and b, representing one infant with and one infant without FMs,

Table 1
Between-group differences between present and absent FMs in variables derived from the GMT.

	Present FMs (110)	Absent FMs (27)	Between-group differences	
	Mean (SE)	Mean (SE)	*p*-value	95% CI
Q_{mean} (%)	2.95 (0.15)	1.79 (0.17)	<.001	(0.71, 1.62)
Q_{max} (%)	32.70 (1.87)	29.04 (2.70)	.269	(−2.92, 10.24)
Q_{SD} (%)	3.20 (0.13)	2.41 (0.17)	<.001	(0.37, 1.22)
Cx_{mean}	4.65 (0.06)	4.49 (0.15)	.328	(−0.17, 0.50)
Cy_{mean}	4.31 (0.06)	4.01 (0.17)	.107	(−0.69, 6.73)
C_{SD}	2.17 (0.05)	2.82 (0.10)	<.001	(−0.09, −0.04)
V_{SD}	6.35 (0.18)	8.29 (0.42)	<.001	(−2.86, −1.01)
A_{SD}	1.03 (0.03)	1.35 (0.07)	<.001	(−0.48, −0.17)

Q_{mean} = quantity of motion mean; Q_{max} = quantity of motion maximum; Q_{SD} = quantity of motion standard deviation; Cx_{mean} = centroid of motion in *x*-direction mean; Cy_{mean} = centroid of motion in *y*-direction mean; C_{SD} = centroid of motion standard deviation; V_{SD} = velocity standard deviation; A_{SD} = acceleration standard deviation.

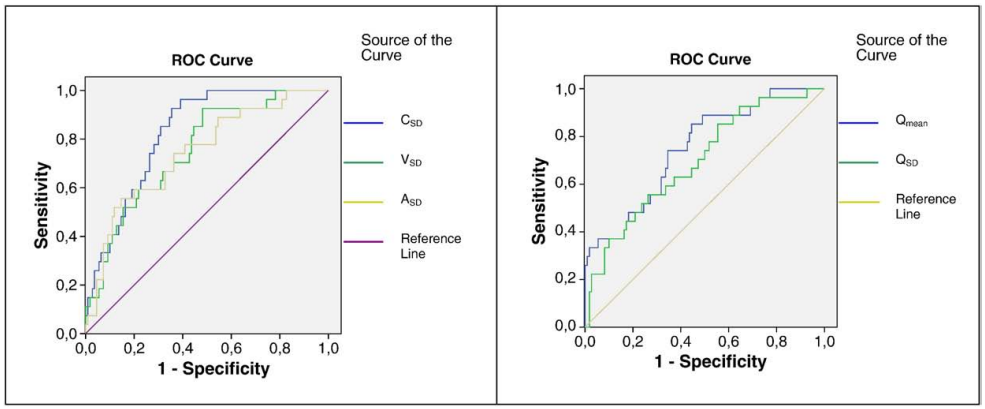

Fig. 4. Receiver operating characteristic curves for the FM diagnostic variables C_{SD}, V_{SD}, A_{SD}, and Q_{mean}, Q_{SD}.

respectively. By observing the original video and the motiongram in parallel, the sequence displayed in the motiongram in Fig. 3a was described as follows by a GM observer (LA): a) ongoing FMs with small amplitude in both arms, little movements in legs, b) leg lifts with flexed knees and some minor arm movements, c) almost no spontaneous movements present, d) ongoing FMs involving the whole body, e) a short pause in the leg movements, and f) continuation of FMs. The video sequence in Fig. 3b without FMs was described as follows: a) spontaneous movements with some leg kicking and synchronized swiping movements in both arms, b) stiff legs that are not moving and minor cramped-synchronized movements in arms, c) some spontaneous, but monotonous movements in all extremities, d) infant is not moving and lies in a stiff, cramped position, e) cramped-synchronized movements in arms and no leg movements, and f) one single synchronous leg kick in addition to the cramped-synchronized arm movements.

Despite the impression of similar motiongrams at the start of the sequences in Fig. 3a and b, specific differences can easily be identified. In sequence 3a, which was a representative motiongram of infants with FMs, there were fewer periods with no movement at all, and during periods of movement, the motiongram density was higher and more evenly distributed. This indicates a motiongram pattern corresponding to clinical observations of a fluent movement pattern with simultaneous movements of neck, trunk and limbs in infants with FMs.

By observing the displays of quantity of motion (Fig. 1) in two infants with present and absent FMs, respectively, the infant with FMs had more overall movements with motions distributed in a regular or cyclic manner. In the display of centroid of motion (Fig. 1) from the infant with FMs, the space covered by the centroid movements was smaller and more circular than the infant without FMs. Furthermore, the infant with absent FMs had a more asymmetrical shape of the total distribution of movements and a larger total area covered by movements.

Table 2
Specificity and area under the curve for variables derived from GMT when sensitivity was set to 81.5%.

	Sensitivity	Specificity	AuC	CI95%	Threshold
Q_{mean}	81.5	44.4	0.75	(0.65, 0.85)	1.46
Q_{SD}	81.5	44.4	0.70	(0.59, 0.81)	2.14
V_{SD}	81.5	56.0	0.75	(0.66, 0.85)	6.37
A_{SD}	81.5	46.4	0.74	(0.64, 0.85)	0.97
C_{SD}	81.5	70.0	0.83	(0.75, 0.90)	2.32

AuC = area under curve; Q_{mean} = quantity of motion mean; Q_{SD} = quantity of motion standard deviation; V_{SD} = velocity of motion standard deviation; A_{SD} = acceleration of motion standard deviation; C_{SD} = centroid of motion standard deviation.

Three quantity of motion and five centroid of motion variables with area under curve values above 0.70 in ROC plots were chosen for further analyses (Table 1). Recordings with absent FMs had significantly lower mean quantity of motion but higher variability of the centroid of motion, acceleration and velocity than infants with present FMs. ROC curves for variables that were significantly different between groups are plotted in Fig. 4. The area under the curve and comparable sensitivity and specificity values for all the variables are shown in Table 2. Logistic regression on each of the movement variables demonstrated that variability of centroid of motion had the strongest association with the absence of FMs. Neither length of video recording or age at time of assessment correlated with variability of centroid of motion ($r = 0.01$ and $r = 0.04$, respectively). Using a combination of movement variables as independent variables did not change the variability of the model ($R^2 = 0.30$), and thus only variability of the centroid of motion was used in the further analyses.

For the variability of centroid of motion, a sensitivity of 81.5% corresponded to a specificity of 70.0% for the detection of absent FMs. A triage method, where results between the set thresholds indicate need for referral to clinical GMA, was applied in order to improve the accuracy. Upper and lower triage thresholds of 90% sensitivity and specificity were chosen, resulting in 20 recordings (15%) falling above upper threshold and 73 (53%) falling below lower threshold. Hence, 44 recordings were regarded as being in need of referral. Lowering the specificity to 80% resulted in 26 recordings which needed referral to further GMA assessment. The numbers of video recordings falling into each triage group, and the number of recordings in need for referral to clinical GMA with two different pair of thresholds, are shown in Table 3.

Table 3
Triage threshold analysis of variability of the centroid of motion (C_{SD}).

Thresholds C_{SD}	Spec: 90% / Sens: 90%	Spec: 80% / Sens: 90%
–Upper	2.93	2.67
–Lower	2.24	2.24
	Number of video recordings	
Above upper threshold: follow-up/treat		
Absent FMs	9	16
Present FMs	11	22
Between thresholds: refer		
Absent FMs	16	9
Present FMs	28	17
Below lower threshold: reassure		
Absent FMs	2	2
Present FMs	71	71
Referral rate	32.1%	19.0%

4. Discussion

The custom-built GMT proved to be a feasible method to generate qualitative and quantitative data based on video recordings of general movements in young infants. Visual representations of the quantity of motion, centroid of motion and motiongrams in particular, can be used for visualisation and qualitative analysis of FMs. Furthermore, quantitative analysis of the variability of centroid of movement proved to be an objective measure to classify the absence or presence of FMs. By employing the GMT in a triage role, the need for further referral could be reduced to 30%. To the best of our knowledge, this is the first study to demonstrate a computer-based method for classification of infants' FMs.

A motiongram is based on a simple reduction of the original motion image, and there is no specific analysis taking place in this process [24]. The presence of observable FMs in the infant's movement repertoire corresponded to recognisable patterns in the motiongram. A continuous motiongram pattern with high density and smooth distribution was present in the sequences containing FMs, giving the impression of a harmonic and periodical movement pattern. The visualisation of quantity of motion showed similar patterns appearing in a regular and smoothly distributed way. The centroid of motion in infants with FMs appeared in a circular manner with small amplitude, continuously making small changes in different directions. Larger amplitudes and less variation of the centroid of motion corresponded to a more monotonous and stereotype movement pattern in infants without FMs. Hence, it can be argued that all GMT qualitative representations reflect some of the significant qualities observed by a GMA observer when classifying present FMs. Whether visual observation of motiongrams may provide assistance to the clinical GMA, must be a subject for further research.

Quantitative features reflecting overall movements were analysed. The mean values of quantity of motion discriminated between infants with and without FMs, demonstrating that the amount of movement is significant. In 3- to 6-month-old infants the FMs are described to superimpose concurrent movements [14]. Whether higher mean quantity of motion values expresses FMs only or also concurrent movements cannot be concluded based on the present study. Larger variability of centroid of motion values in infants with absent FMs, may suggest a less stable movement pattern where the centroid of motion changes more over time. The variation in velocity and acceleration of the centroid of motion also discriminated between groups and may possibly be related to movement fluency. However, these outcomes did not improve the sensitivity of the method beyond the variability of the centroid of motion.

The length of the edited video recording used for analysis did not influence the GMT classification results. A minimum of 30 s per edited recording length was long enough to capture and classify features specific for FMs, suggesting a robust computer-based method. Neither did the age at the time of recording influence the results. This confirms that the age range chosen in the present study (10–18 weeks) was well within the age range defined as fidgety movements' age by Prechtl et al. [14].

Recently a relationship between GMs and cerebral white matter abnormalities on MRI has been demonstrated. In very preterm infants (<30 weeks gestation), abnormal FMs at 3 months correlated with white matter abnormality on MRI, suggesting that abnormal FMs reflect white matter injury [1]. Despite MRI obtained without sedation and anesthesia, the MRI method is expensive and not easily accessible. MRI qualitative scoring of white matter abnormalities requires top competence and will be limited to certain centres. The GMT is non-intrusive and based on an already established clinical method of evaluating infants' general movements. It is easy to use and requires little training. One day was sufficient to manage the software application, and results of the analysis were available after 10–15 min. This study represents the first evaluation of a new method, and it will need further development for general clinical use. The GMT may provide assistance for more focused follow-up programs for those with very high probability of developing CP. It may also be a valuable tool for research on early intervention programs for high-risk infants.

The population in our study is a convenience sample of infants with a high prevalence of absent FMs (19.7%). Referral rate using the triage model will differ depending on the prevalence of disease in the population studied. The results must, therefore, be interpreted with caution, and studies on well-defined, high-risk populations must be carried out. Long term neurological outcome was not yet collected at the time of the present study. A previous study by our group, however, has demonstrated a very high correlation between absent FMs and CP at 2 years follow-up [11]. It is therefore a reason to believe that absent FMs in this study predict later CP.

5. Conclusion

The present study demonstrates a novel, non-intrusive and easily applicable computer-based method to identify the presence of FMs in young infants. A motiongram based on a video recording displayed similar qualitative features as the clinical GMA. Quantitative features related to the quantity of motion and the variability of the centre of movement, were significantly associated with the presence of FMs. More studies are needed on well-defined high-risk populations. The accuracy of CP prediction using the GMT must be assessed in future studies with long-term neurological outcome.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.

163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS

193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN

218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL
224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA
244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES

245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

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248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS
251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257. Erik Skaaheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS
260. Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT
262. Ole Johan Kemi: ON THE CELLULAR BASIS OF AEROBIC FITNESS, INTENSITY-DEPENDENCE AND TIME-COURSE OF CARDIOMYOCYTE AND ENDOTHELIAL ADAPTATIONS TO EXERCISE TRAINING
263. Eszter Vanky: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN PREGNANCY
264. Hild Fjærtoft: EXTENDED STROKE UNIT SERVICE AND EARLY SUPPORTED DISCHARGE. SHORT AND LONG-TERM EFFECTS
265. Grete Dyb: POSTTRAUMATIC STRESS REACTIONS IN CHILDREN AND ADOLESCENTS
266. Vidar Fykse: SOMATOSTATIN AND THE STOMACH
267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

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269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE
271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT
272. Therese Standal: MULTIPLE MYELOMA: THE INTERPLAY BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MARROW MICROENVIRONMENT

273. Ingvild Saltvedt: TREATMENT OF ACUTELY SICK, FRAIL ELDERLY PATIENTS IN A GERIATRIC EVALUATION AND MANAGEMENT UNIT – RESULTS FROM A PROSPECTIVE RANDOMISED TRIAL
274. Birger Henning Endreseth: STRATEGIES IN RECTAL CANCER TREATMENT – FOCUS ON EARLY RECTAL CANCER AND THE INFLUENCE OF AGE ON PROGNOSIS
275. Anne Mari Aukan Rokstad: ALGINATE CAPSULES AS BIOREACTORS FOR CELL THERAPY
276. Mansour Akbari: HUMAN BASE EXCISION REPAIR FOR PRESERVATION OF GENOMIC STABILITY
277. Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULITCENTRE RANDOMISED STUDIES
278. Hilde Pleym: BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY - STUDIES ON HEMOSTATIC MECHANISMS, PROPHYLACTIC DRUG TREATMENT AND EFFECTS OF AUTOTRANSFUSION
279. Line Merethe Oldervoll: PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS IN CANCER PATIENTS
280. Boye Welde: THE SIGNIFICANCE OF ENDURANCE TRAINING, RESISTANCE TRAINING AND MOTIVATIONAL STYLES IN ATHLETIC PERFORMANCE AMONG ELITE JUNIOR CROSS-COUNTRY SKIERS
281. Per Olav Vandvik: IRRITABLE BOWEL SYNDROME IN NORWAY, STUDIES OF PREVALENCE, DIAGNOSIS AND CHARACTERISTICS IN GENERAL PRACTICE AND IN THE POPULATION
282. Idar Kirkeby-Garstad: CLINICAL PHYSIOLOGY OF EARLY MOBILIZATION AFTER CARDIAC SURGERY
283. Linn Getz: SUSTAINABLE AND RESPONSIBLE PREVENTIVE MEDICINE. CONCEPTUALISING ETHICAL DILEMMAS ARISING FROM CLINICAL IMPLEMENTATION OF ADVANCING MEDICAL TECHNOLOGY
284. Eva Tegnander: DETECTION OF CONGENITAL HEART DEFECTS IN A NON-SELECTED POPULATION OF 42,381 FETUSES
285. Kristin Gabestad Nørsett: GENE EXPRESSION STUDIES IN GASTROINTESTINAL PATHOPHYSIOLOGY AND NEOPLASIA
286. Per Magnus Haram: GENETIC VS. AQUIRED FITNESS: METABOLIC, VASCULAR AND CARDIOMYOCYTE ADAPTATIONS
287. Agneta Johansson: GENERAL RISK FACTORS FOR GAMBLING PROBLEMS AND THE PREVALENCE OF PATHOLOGICAL GAMBLING IN NORWAY
288. Svein Artur Jensen: THE PREVALENCE OF SYMPTOMATIC ARTERIAL DISEASE OF THE LOWER LIMB
289. Charlotte Björk Ingul: QUANITIFICATION OF REGIONAL MYOCARDIAL FUNCTION BY STRAIN RATE AND STRAIN FOR EVALUATION OF CORONARY ARTERY DISEASE. AUTOMATED VERSUS MANUAL ANALYSIS DURING ACUTE MYOCARDIAL INFARCTION AND DOBUTAMINE STRESS ECHOCARDIOGRAPHY
290. Jakob Nakling: RESULTS AND CONSEQUENCES OF ROUTINE ULTRASOUND SCREENING IN PREGNANCY – A GEOGRAPHIC BASED POPULATION STUDY
291. Anne Engum: DEPRESSION AND ANXIETY – THEIR RELATIONS TO THYROID DYSFUNCTION AND DIABETES IN A LARGE EPIDEMIOLOGICAL STUDY
292. Ottar Bjerkeset: ANXIETY AND DEPRESSION IN THE GENERAL POPULATION: RISK FACTORS, INTERVENTION AND OUTCOME – THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
293. Jon Olav Drogset: RESULTS AFTER SURGICAL TREATMENT OF ANTERIOR CRUCIATE LIGAMENT INJURIES – A CLINICAL STUDY
294. Lars Fosse: MECHANICAL BEHAVIOUR OF COMPACTED MORSELLISED BONE – AN EXPERIMENTAL IN VITRO STUDY
295. Gunilla Klensmeden Fosse: MENTAL HEALTH OF PSYCHIATRIC OUTPATIENTS BULLIED IN CHILDHOOD
296. Paul Jarle Mork: MUSCLE ACTIVITY IN WORK AND LEISURE AND ITS ASSOCIATION TO MUSCULOSKELETAL PAIN
297. Björn Stenström: LESSONS FROM RODENTS: I: MECHANISMS OF OBESITY SURGERY – ROLE OF STOMACH. II: CARCINOGENIC EFFECTS OF *HELICOBACTER PYLORI* AND SNUS IN THE STOMACH

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298. Haakon R. Skogseth: INVASIVE PROPERTIES OF CANCER – A TREATMENT TARGET ? IN VITRO STUDIES IN HUMAN PROSTATE CANCER CELL LINES
299. Janniche Hammer: GLUTAMATE METABOLISM AND CYCLING IN MESIAL TEMPORAL LOBE EPILEPSY
300. May Britt Drugli: YOUNG CHILDREN TREATED BECAUSE OF ODD/CD: CONDUCT PROBLEMS AND SOCIAL COMPETENCIES IN DAY-CARE AND SCHOOL SETTINGS
301. Arne Skjold: MAGNETIC RESONANCE KINETICS OF MANGANESE DIPYRIDOXYL DIPHOSPHATE (MnDPDP) IN HUMAN MYOCARDIUM. STUDIES IN HEALTHY VOLUNTEERS AND IN PATIENTS WITH RECENT MYOCARDIAL INFARCTION
302. Siri Malm: LEFT VENTRICULAR SYSTOLIC FUNCTION AND MYOCARDIAL PERFUSION ASSESSED BY CONTRAST ECHOCARDIOGRAPHY
303. Valentina Maria do Rosario Cabral Iversen: MENTAL HEALTH AND PSYCHOLOGICAL ADAPTATION OF CLINICAL AND NON-CLINICAL MIGRANT GROUPS
304. Lasse Løvstakken: SIGNAL PROCESSING IN DIAGNOSTIC ULTRASOUND: ALGORITHMS FOR REAL-TIME ESTIMATION AND VISUALIZATION OF BLOOD FLOW VELOCITY
305. Elisabeth Olstad: GLUTAMATE AND GABA: MAJOR PLAYERS IN NEURONAL METABOLISM
306. Lilian Leistad: THE ROLE OF CYTOKINES AND PHOSPHOLIPASE A_2S IN ARTICULAR CARTILAGE CHONDROCYTES IN RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS
307. Arne Vaaler: EFFECTS OF PSYCHIATRIC INTENSIVE CARE UNIT IN AN ACUTE PSYCIATHRIC WARD
308. Mathias Toft: GENETIC STUDIES OF LRRK2 AND PINK1 IN PARKINSON'S DISEASE
309. Ingrid Løvold Mostad: IMPACT OF DIETARY FAT QUANTITY AND QUALITY IN TYPE 2 DIABETES WITH EMPHASIS ON MARINE N-3 FATTY ACIDS
310. Torill Eidhammer Sjøbakk: MR DETERMINED BRAIN METABOLIC PATTERN IN PATIENTS WITH BRAIN METASTASES AND ADOLESCENTS WITH LOW BIRTH WEIGHT
311. Vidar Beisvåg: PHYSIOLOGICAL GENOMICS OF HEART FAILURE: FROM TECHNOLOGY TO PHYSIOLOGY
312. Olav Magnus Søndenå Fredheim: HEALTH RELATED QUALITY OF LIFE ASSESSMENT AND ASPECTS OF THE CLINICAL PHARMACOLOGY OF METHADONE IN PATIENTS WITH CHRONIC NON-MALIGNANT PAIN
313. Anne Brantberg: FETAL AND PERINATAL IMPLICATIONS OF ANOMALIES IN THE GASTROINTESTINAL TRACT AND THE ABDOMINAL WALL
314. Erik Solligård: GUT LUMINAL MICRODIALYSIS
315. Elin Tollefsen: RESPIRATORY SYMPTOMS IN A COMPREHENSIVE POPULATION BASED STUDY AMONG ADOLESCENTS 13-19 YEARS. YOUNG-HUNT 1995-97 AND 2000-01; THE NORD-TRØNDELAG HEALTH STUDIES (HUNT)
316. Anne-Tove Brenne: GROWTH REGULATION OF MYELOMA CELLS
317. Heidi Knobel: FATIGUE IN CANCER TREATMENT – ASSESSMENT, COURSE AND ETIOLOGY
318. Torbjørn Dahl: CAROTID ARTERY STENOSIS. DIAGNOSTIC AND THERAPEUTIC ASPECTS
319. Inge-Andre Rasmussen jr.: FUNCTIONAL AND DIFFUSION TENSOR MAGNETIC RESONANCE IMAGING IN NEUROSURGICAL PATIENTS
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