Putative neural substrate of normal and abnormal general movements

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Abstract

During the last decade it has become clear that the assessment of the quality of general movements (GMs) in foetus and young infant is a sensitive tool to evaluate the integrity of the young nervous system. GMs are movements in which all parts of the body participate. The hallmark of typical GMs is movement complexity and variation; in abnormal GMs movement complexity and variation is reduced or absent. Abnormal GMs may predict developmental outcome. Prediction on the basis of longitudinal series of GM assessments is best. Second best is prediction on the basis of an assessment at ‘fidgety’ GM age, i.e. at 2–4 months post-term. Definitely abnormal GMs at ‘fidgety’ age are related to cerebral palsy, mildly abnormal GMs to minor neurological dysfunction at school age. In the present paper the hypothesis is advanced that GM complexity and variation are brought about by the transiently present cortical subplate and that abnormal GMs are the result of damage or dysfunction of the subplate and its efferent motor connections in the periventricular white matter.

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Keywords: General movements; Cerebral palsy; Subplate; Periventricular white matter; Minor neurological dysfunction

1. Evolution in the understanding of motor development

During the last century knowledge on mechanisms governing the functions of the central nervous system rapidly increased. The expansion in knowledge was brought about by the development of sophisticated genetic, physiological, neurochemical, and imaging techniques. In the field of motor control the augmented understanding of neurophysiology resulted in a gradual shift from the concept that motor behaviour is largely controlled by reflex mechanisms (Sherrington, 1906; Magnus and De Kleijn, 1912) 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 (Grillner et al., 1995). For instance, nowadays it is assumed that motor control of rhythmical
movements like locomotion, respiration, sucking, and mastication is based on the so-called central pattern generators (CPGs). CPGs are neural networks that are able to coordinate autonomously, i.e. without segmental sensory or supraspinal information, the activity of many muscles. To drive CPG activity a minimal sensory input or a minimum level of neuroactive substances such as serotonin or excitatory amino acids is required (Cazalets et al., 1992). Of course, in typical conditions the CPG network does not work autonomously, but is affected by signals from other parts of the nervous system. The activity of the networks, which are usually located in the spinal cord or brain stem, is controlled from supraspinal areas via descending motor pathways (Grillner et al., 1995). Supraspinal activity itself is organized in large-scale networks, in which cortical areas are functionally connected through direct recursive interaction or through intermediary cortical or subcortical (striatal, cerebellar) structures (Alexander and Crutcher, 1990; Hikosaka et al., 1992). Of course, in typical conditions the CPG network does not work autonomously, but is affected by signals from other parts of the nervous system. The activity of the networks, which are usually located in the spinal cord or brain stem, is controlled from supraspinal areas via descending motor pathways (Grillner et al., 1995).

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The concept of spontaneous activity has been developed by many authors, including Alexander and Crutcher (1990) and Hikosaka et al. (1992). Development is currently viewed as a complex process in which genetically based and environmentally driven processes continuously interact (Thelen, 1995; Hadders-Algra, 2000a). Recognition of the fact that spontaneous activity is a fundamental characteristic of developing neuronal networks made clinicians realize that the observation of spontaneous motor behaviour might offer additional means to assess neurological integrity in children (Prechtl, 1990, 2001; Hadders-Algra, 2005).

Spontaneously generated activity is a widespread phenomenon in the developing nervous system (Feller, 1999; O’Donovan, 1999). Interestingly, the basic features of spontaneous activity are similar across the nervous system: it consists of rhythmic bursts of action potentials which are correlated across tens or hundreds of cells and occur with a periodicity in the order of minutes (Feller, 1999). Presumably the periodicity is the result of activity in networks with highly interconnected excitatory synapses (O’Donovan, 1999; Hanson and Landmesser, 2003). A network of spontaneously active cells connected through purely excitatory synapses has a steady increase of activity till a certain threshold is reached. An episode of correlated firing follows, which in turn induces network depression. When network activity subsequently has reached a critically low point, the cycle of spontaneous activity starts again (O’Donovan and Chub, 1997; O’Donovan, 1999). Spontaneously generated neural activity has various functional consequences, such as the production of spontaneous motility and the establishment and maintenance of cortical networks during developmental phases when sensory input cannot yet be processed properly (Penn and Shatz, 1999; Khazipov and Luhmann, 2006).

Prechtl (1990) was amongst the pioneers promoting the evaluation of the quality of spontaneous motility during early human development. He discovered that the quality of spontaneous movements of the foetus and young infant, i.e. the quality of general movements (GMs), may provide information on the integrity of the young nervous system. GMs consist of series of gross movements of variable speed and amplitude, which involve all parts of the body but lack a distinctive sequencing of the participating body parts (Prechtl and Nolte, 1984; Prechtl, 1990). The movements wax and wane in intensity, force and speed, and their onset and end are gradual, a description which perfectly matches the above described behaviour of spontaneous activity in developing neural networks (O’Donovan, 1999). GMs are present from early foetal life till about 3–4 months post-term (Prechtl, 1990; Hadders-Algra, 2004).

The aim of the present paper is to describe typical GM development and the clinical picture of abnormal GMs and to discuss possibly underlying neural mechanisms of normal and abnormal GMs.

2. Typical development of GMs

2.1. Observational data

A recent, detailed ultrasound study on the emergence of foetal motility revealed that the earliest movements can be observed at the age of 7 weeks and 2 days postmenstrual age (PMA,1 Lu¨ chinger et al., 2007). The ages of the foetuses studied were known exactly as the foetuses had been conceived by means of in vitro fertilization. The first movements observed were slow, small sideways bending movements of head and/or trunk. This means that the earliest movements of the foetus consist of slow, small, non-complex, and isolated movements of the proximal parts of the body. The study showed that a few days later, the simple and stereotyped movements developed into movements in which also one or two arms or legs participated. But the movements continued to be slow, small, simple, and stereotyped. At the age of 9–10 weeks PMA GMs—consisting of movements in which all parts of the body participate—emerged. With the emergence of GMs the relatively simple sideways bending movements disappeared. Initially, GMs showed little variation in movement direction, amplitude, and speed. But after a

1Human pregnancy lasts about 280 days (40 weeks) calculated from the first day of the last menstrual period (Smith, 2001). Obstetricians invariably use PMA to indicate foetal age, whereas neuroscientists studying foetal brain development use postconceptional age based on foetal crown-rump length. However, in many studies on structural brain development in pre-term infants PMA is used interchangeably with postconceptional age. This means that the literature on human brain development between 20 and 40 weeks PMA is hampered by a systematic confusion of 2 weeks.
GMs show age-specific characteristics (Table 1). Little is known on the age-specific changes of GMs during the first two trimesters of pregnancy. During the third trimester GMs are characterized by a large variation and complexity. The movements—described as ‘pre-term’ GMs (Hadders-Algra et al., 1997)—give the impression of a wonderfully complex ballet performance and include many movements of the trunk. Around 36–38 weeks PMA a transition in GMs can be observed. The largely variable ‘pre-term’ GMs change into the more slow and forceful ‘writhing’ GMs, in which the trunk participates less obviously than during the previous GM phase (Hadders-Algra et al., 1997). The ‘writhing’ GMs constitute a temporary form of GMs, as they disappear around 6–8 weeks post-term age. The ‘writhing’ GMs are replaced by the final form of GMs, the so-called ‘fidgety’ GMs. ‘Fidgety’ GMs consist of a continuous stream of tiny, elegant movements occurring irregularly all over the body (Prechtl and Hopkins, 1986; Hadders-Algra and Prechtl, 1992). The ‘fidgety’ GMs disappear around 4 months post-term. They are gradually replaced by goal-directed movements, such as voluntarily manipulative finger movements and reaching movements (Hopkins and Prechtl, 1984).

2.2. Putative neural mechanisms underlying typical GM development

The finding that the first movements emerge at 7 weeks and 2 days means that they develop prior to the completion of the spinal reflex arc, which—according to the limited information available—is accomplished at 8 weeks PMA (Okado and Kojima, 1984). This underscores the spontaneous or autogenic nature of the first movements (Preyer, 1885; Hooker, 1952; Hall and Oppenheim, 1987). The developmental sequence of sideways bending movements of head and/or trunk followed by movements in which increasingly more parts of the body participate corresponds to findings in many animal species such as fish (Preyer, 1885), amphibian (Preyer, 1885; Coghill, 1929), guinea pig (Preyer, 1885; Carmichael, 1970), and rat (Angulo Y González, 1932). It could be surmised that the first movements, i.e. the sideways bending movements of head and trunk, are generated by neuronal networks—CPG networks—in the spinal cord and brain stem (Hanson and Landmesser, 2003). In all species mentioned the lateral flexion movements of head and/or trunk are followed by movements in which all parts of the body participate. However, whether the generalized motor behaviour in non-human species includes movement variation and complexity is unclear, as the description of motility generally has been restricted to whether or not specific body parts participate in the movement. The exception to this rule is Hamburger’s (1973) description of chick embryo behaviour. He noted that the generalized motility of the chick embryo is monotonous and lacks rotatory components, i.e. it lacks the typical components of human GM activity.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Age-specific characteristics of normal GMs (Hadders-Algra and Prechtl, 1992; Hadders-Algra et al., 1997)</th>
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<tr>
<td>GM type</td>
<td>Period of presence in weeks PMA</td>
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<tr>
<td>Pre-term GMs</td>
<td>From +28 weeks</td>
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<tr>
<td>Writhing GMs</td>
<td>From 36 to 38 weeks Till 46–52 weeks</td>
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<tr>
<td>Fidgety GMs</td>
<td>From 46 to 52 weeks Till 54–58 weeks</td>
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At any GM age, the basic characteristics of normal GMs are (1) participation of all body parts and (2) movement complexity and variation.

Few days, the majority of GMs showed a substantial degree of variation in speed, amplitude, participating body parts, and movement direction. The results of this ultrasound study correspond remarkably well to the data reported by Hooker (1952, 1958). Hooker studied motor behaviour in human foetuses secured by hysterotomy or hysterectomy. He observed motor behaviour and elicited reflexes by means of stroking restricted areas of skin with a human or horse hair. He noted earliest motor behaviour after stroking the perioral region. Like Lückinger et al. (2007), Hooker recorded that the first movements could be observed at 7–8 weeks PMA. They consisted of lateral bending movements of head or trunk. He noticed that a week later also the arms participated. At the age of 9–10 weeks movements became more complex and included rotatory movements of the trunk.

GMs continue to be present throughout pregnancy and during the first months after term age. Interestingly, GM activity is the most prevalent type of motor behaviour of foetus and young infant (De Vries et al., 1982; Hadders-Algra, 2004). The incidence of GMs is relatively stable till 28–32 weeks PMA (De Vries et al., 1982, 1985). Thereafter the incidence decreases—a decrease which has been observed in utero (Roodenburg et al., 1991) and in pre-term infants (Prechtl et al., 1979). It should, however, be stressed that throughout pre- and postnatal life the incidence of GMs is characterized by a large intra- and interindividual variation (De Vries et al., 1985; Cioni et al., 1989; Cioni and Prechtl, 1990; Roodenburg et al., 1991).
Interestingly, the emergence of variable and complex GMs at weeks 9–10 PMA coincides with the appearance of neurons with synaptic vesicles suggestive of synaptic activity in the cortical subplate (Molliver et al., 1973; Supér et al., 1998). The subplate is a transient structure which lies between the intermediate zone, i.e. the periventricular white matter, and the developing cortical plate (Kostovic and Rakic, 1990; Allendoerfer and Shatz, 1994; Kostovic and Judas, 2006, 2007). The subplate is the earliest maturing cortical structure. It has three major functions. First, it plays a role in pioneering descending corticothalamic pathways through the internal capsule and other intracortical pathways (McConnell et al., 1989; Allendoerfer and Shatz, 1994). Second, it functions as a 'waiting room' and temporary goal of afferent fibres originating from the thalamus, contra- and ipsilateral hemispheres, basal forebrain, and monoaminergic brainstem nuclei heading for a cortical destination. The temporary connections in the subplate form functionally active circuitries, presumably playing an important role in the mediation of foetal behaviour such as GM activity (Allendoerfer and Shatz, 1994; Hanganu et al., 2002).

Third, evidence is accumulating that subplate neurons play a role in the fine-tuning of cortical connectivity (Allendoerfer and Shatz, 1994). For instance, ablation of subplate neurons prevents the formation of ocular dominance columns in the visual cortex, a developmental deviation which is associated with reduced capacities to process visual information (Kalnol et al., 2003).

The coincidence of the emergence of the features which are most typical for human GMs, i.e. movement complexity and variation, with the emergence of synaptic activity in the subplate might indicate that this transient cortical structure plays a pivotal role in the generation of GM complexity and variation. The hypothesis presupposes that the subplate has descending projections which may directly or indirectly transmit information to the CPG networks in the brainstem and spinal cord. Information on these descending projections is, however, limited. It is known that the subplate from early age onwards does not only contain locally projecting interneurons but also neurons with long-distance projections, e.g. projections to the thalamus using excitatory amino acids (McConnell et al., 1989; Antonini and Shatz, 1990; Kostovic and Judas, 2007). In addition, studies in the foetal rat indicated that descending supraspinal pathways emerge prior to and coincident with the emergence of subplate neurons at embryonic day 16 (Baislev et al., 1996; Lakke, 1997; De Boer-van Huizen and Ten Donkelaar 1999). Thus, it is conceivable that the subplate induces movement complexity and variation and that this information is transmitted initially via polysynaptic pathways to the CPG networks in the brainstem and spinal cord. From about 24 weeks PMA also direct corticospinal connections may contribute to the communication between subplate and spinal cord (Eyre, 2007). Two other arguments are in favour of the hypothesis that the subplate plays a pivotal role in the generation of GM complexity and variation. First, it might be that the typical human (or primate) developmental feature of complex and variable GMs is related to another typical human (or primate) developmental characteristic, i.e. the prominent presence of the subplate. In no other species than man the subplate is so large and present for such a long developmental period. The size of the subplate relatively to the cortical plate increases spectacularly as one ascends the phylogenetic scale: in rodents the ratio of subplate area to cortical plate area is 1:2, whereas in the human it reaches 4:1 (Kostovic and Rakic, 1990; Allendoerfer and Shatz, 1994). Second, the evolution of the subplate neatly matches that of GM development. Subplate activity emerges when GM complexity and variation emerge. The subplate is particularly present when GMs bloom, i.e. between 24 and 36 weeks PMA (Kostovic and Rakic, 1990; Kostovic and Judas, 2006, 2007). The gradual disappearance of the subplate between 36 weeks PMA and 3–6 months post-term (Krmpotic-Nemanic et al., 1988) parallels the final phases of GM development. During the last phases of GM development remnants of subplate neurons can be found as interstitial neurons in the periventricular white matter (Kostovic and Rakic, 1980). The dissolution of the subplate indicates that the balance between endogenously driven cortical activity slowly shifts to environmentally driven activity mediated by thalamocortical connections (Khazipov and Luhmann, 2006; Kostovic and Judas, 2006; Vanhatalo and Kaila, 2006). Indeed, prior to 4 months post-term infants only have a limited capacity to adapt motor behaviour to environmental conditions: it is restricted to adaptation of single limb movements (Van der Meer et al., 1995; Angulo-Kinzler et al., 2002; Nagy et al., 2005). Young infants are not able to modify complex and variable GM motility to environmental constraints (Dibiasi and Einspieler, 2004; De Graaf-Peters et al., 2006). After the age of 3 months, infants may use environmental information to increase movement variation in supine or to select an efficient postural strategy out of a repertoire of postural adjustments (De Graaf-Peters et al., 2006, 2007).

The ‘writhing’ GM phase starts at 36–38 weeks PMA, i.e. at a point in time at which the subplate has shrunk considerably, a process which is paralleled by the ingrowth of callosal and long cortico-cortical pathways into the cortex (Kostovic and Jovanov-Milosevic, 2006; Kostovic and Judas, 2007). The age of 36–38 weeks PMA is also the age at which clearly defined behavioural states emerge (Nijhuis et al., 1982) and the slow activity transient characteristics of the pre-term EEG disappear (Vanhatalo et al., 2005; Vanhatalo and Kaila, 2006). Vanhatalo et al. (2005) suggested that the latter developmental changes might be related to the functional change of γ-aminobutyric acid (GABA) from excitatory to inhibitory (cf. Dupont et al., 2006). However, the change in GABA function is not the only change in cortical neurotransmitter systems occurring near term; also the glutamate system exhibits developmental changes. During...
the peri-term period, i.e., the period between 36 and 38 weeks PMA and 6–8 weeks post-term, cortical glutamate receptors are transiently overexpressed (McDonald and Johnston, 1990; De Graaf-Peters and Hadders-Algra, 2006). It is conceivable that the glutamate receptor overexpression is the cortical correlate of the increased motoneuronal excitability observed during the peri-term period (Hakamada et al., 1988; Hadders-Algra et al., 1992, 1997).

After the peri-term period of ‘writhing’ GMs and increased excitability the final GM phase of ‘fidgety’ activity is reached. Surface EMG recordings indicated that the change of ‘writhing’ GMs into ‘fidgety’ GMs is associated with a decrease in the duration and amplitude of the phasic EMG bursts and a decrease in tonic background activity. Our group suggested that the EMG changes might point to developmental changes of neuronal membranes throughout the nervous system, changes in muscle innervation (a regression of polynuclear muscle innervation), changes in the spinal circuitries (an increasing effect of Renshaw inhibition) and—last but not the least—changes in supraspinal organization (Hadders-Algra et al., 1992; Gramsbergen et al., 1997). The latter idea is supported by imaging studies which indicated that around the age of 3 months post-term functional activity in the cerebellum, basal ganglia, and parietal, temporal, and occipital cortices increases significantly (Chugani et al., 1987; Rubinstein et al., 1989). It might be—as argued above—that the dissolution of the cortical subplate plays a pivotal role in the major neurodevelopmental transformation occurring around 3 months post-term: a transformation during which GM activity is replaced by goal-directed activity.

3. Abnormal GMs

3.1. The clinical picture of abnormal GMs

Keywords to describe the quality of GMs are variation and complexity (Prechtl, 1990, 2001; Hadders-Algra 2001, 2004; Einspieler and Prechtl, 2005). Complexity points to the spatial variation of movements. It is brought about by the independent exploration of degrees of freedom in all body joints. The continuously varying combinations of flexion–extension, abduction–adduction, and endorotation–exorotation produce frequent changes in movement direction of the participating body parts. GM variation represents the temporal variation of movements. It means that, across time, the infant continuously explores the movement possibilities the body offers. Thus, the primary parameters of GM quality in fact evaluate two aspects of movement variation. This fits to the idea that variation is a fundamental feature of the function of the healthy young nervous system and stereotypy a hallmark of early brain dysfunction (Touwen, 1978; Hadders-Algra 2000a, b).

Four classes of GM quality can be distinguished: two forms of normal GMs (normal–optimal and normal–suboptimal GMs) and two forms of abnormal GMs (mildly and definitely abnormal GMs; Table 2). Normal–optimal GMs are abundantly variable and complex. In addition they are also fluent. Normal–optimal movements are relatively rare: only 10–20% of 3 months old term infants show GMs with such a beautiful quality (Bouwstra et al., 2003a; Hornstra et al., 2003). The majority of infants show normal–suboptimal movements, which are sufficiently variable and complex but not fluent. Mildly abnormal GMs are insufficiently variable and complex and not fluent, and definitely abnormal GMs are virtually devoid of complexity, variation, and fluency. It is good to realize, that the classification into four categories of quality is somewhat artificial. In fact, quality of movement is a continuum with at the one extreme splendidly complex, variable, and fluent movements and at the other extreme very stereotyped movements, such as a repertoire restricted to cramped–synchronized movements (Ferrari et al., 1990; Hadders-Algra et al., 1997). The latter movements are characterized by a suddenly occurring en bloc movement, in which trunk and—flexed or extended—limbs stiffly move in utter synchrony. Actually the cramped–synchronized movements are the only form of GMs which can be considered as pathological. Their presence points to a loss of supraspinal control (Hadders-Algra, 1993). Thus, the presence of cramped–synchronized GMs implies that the infant shows abnormal GMs. When an infant only occasionally shows a cramped–synchronized GM within a repertoire of movements which mostly exhibit some degree of variation and complexity, GM quality can be classified as mildly abnormal. But when the infant frequently exhibits the cramped–synchronized pattern, GM quality should be considered as definitely abnormal (Groen et al., 2005).

Various pre-, peri-, and neonatal adversities, such as maternal diabetes, intrauterine growth retardation, preterm birth, perinatal asphyxia, neonatal hyperbilirubinemia, neonatal treatment with dexamethasone, and antenatal exposure to antiepileptic drugs, can give rise to abnormal GMs (Hadders-Algra, 2001; Soorani-Lunsing et al., 2001; Parisi et al., 2003). Definitely abnormal GMs are specifically but not exclusively related to discernible lesions of the brain (Ferrari et al., 1990; Prechtl et al., 1993; Hadders-Algra et al., 1997; Bos et al., 1998).
Mildly abnormal GMs at 3 months post-term are associated with conditions which vary from pre-term birth, intraterine growth retardation, moderate degrees of hyperbilirubinemia at term, and Down’s syndrome to associated with conditions which vary from pre-term birth, M+adly abnormal GMs at 3 months in healthy term infants have been associated with exclusive breastfeeding for at least 6 weeks (Bouwstra et al., 2003b).

Many developmental studies indicated that movement quality is not a fixed phenomenon. It may change in various ways: movement quality can be transiently affected by illness (Bos et al., 1997) and movement abnormalities can vanish or become more distinct with increasing age (Ferrari et al., 1990; Prechtl et al., 1993; Hadders-Algra et al., 2004). The majority of changes in GM quality occur in the transitional periods during which normal GMs change in form, i.e., between 36 and 38 weeks PMA and between 6 and 8 weeks post-term (Hadders-Algra and Groothuis, 1999; Hadders-Algra et al., 2004). Within the three GM phases (Table 1) movement quality is relatively stable.

The predictive validity of GM quality varies with the age at which GMs are evaluated and with the type of outcome. Best prediction is achieved by longitudinal series of GM assessments. Infants who persistently show definitely abnormal GMs, even while passing the transformational phases at 36–38 weeks PMA and 6–8 weeks post-term, have a high risk (70–85%) for the development of cerebral palsy (CP; Ferrari et al., 1990; Prechtl et al., 1993). Infants who persistently show cramped–synchronized GMs invariably develop CP (Ferrari et al., 2002). The prediction of a single GM assessment improves with increasing age. Thus, prediction is best at the age of ‘fidgety’ GMs, i.e. at 2–4 months post-term. Studies in populations of infants at very high risk for developmental disorders reported that the presence of definitely abnormal GMs at ‘fidgety’ age, which implies a total absence of the elegant, dancing complexity of ‘fidgety’ movements, predicts CP with an accuracy of 85–98% (Prechtl et al., 1997; Hadders-Algra et al., 2004). However, a current study on the development of pre-term infants with less risk for developmental disorders than those included in the studies of Prechtl and Hadders-Algra indicates that the risk of the development of CP in infants with definitely abnormal GMs at ‘fidgety’ age is substantially lower than about 90% and lies in the order of 20–25% (Blauw-Hospers et al., 2007). Nevertheless, it should be realized that infants with definitely abnormal GMs at ‘fidgety’ age who do not develop CP in general show other developmental problems, such as minor neurological dysfunction (MND), attention deficit hyperactivity disorder (ADHD), or cognitive problems (Hadders-Algra et al., 2004; Groen et al., 2005; Blauw-Hospers et al., 2007). Mildly abnormal GMs at ‘fidgety’ age are related to the development of MND, in particular to coordination problems and fine manipulative disability, ADHD, and aggressive behaviour (Hadders-Algra and Groothuis, 1999; Hadders-Algra et al., 2004; Groen et al., 2005; Einspieler et al., 2006), but the accuracy to predict these ‘minor’ problems is modest, due to the presence of relatively many false positives, resulting in a moderate specificity. The power to predict ‘minor’ developmental disorders improves considerably when the results of the assessment of GMs are combined with those of the infant neurological examination (Hadders-Algra et al., 2004).

3.2. Putative neural substrate of abnormal GMs

The clinical data indicate that abnormal GMs are related to brain lesions and/or brain dysfunction. An intriguing question is whether abnormal GMs can be attributed to specific dysfunctions of the young brain. If the hypothesis is correct, that GM complexity and variation are generated by the cortical subplate and mediated by the motor efferent connections of the subplate, it would follow that abnormal GMs are the result of damage or dysfunction of the subplate and/or its connections, which run through the periventricular white matter (Kostovic and Judas, 2006; Kostovic and Jovanov-Milosevic, 2006). Subplate and periventricular white matter injury are nowadays considered to be the dominant encephalopathy of premature infants (Volpe 1996, 2003, 2005; McQuillen and Ferriero, 2005). Previously, it was thought that the focal necrotic, cystic lesion of the periventricular white matter (periventricular leukomalacia) was the major neuropahtological problem of pre-term infants. Cystic periventricular leukomalacia occurs in 3–5% of pre-term infants and is strongly associated with the development of CP (Volpe, 2005). But, with the introduction of more precise imaging techniques, it became clear that diffuse, noncystic white matter injury—indicating diffuse damage of axons and oligodendrocytes—is much more common than cystic periventricular leukomalacia. It occurs in 20–50% of the pre-terms born prior to 34 weeks (Volpe, 2003; Counsell et al., 2003). Diffuse periventricular white matter injury in turn is correlated with a significant decrease of cortical grey matter volume at term age (Inder et al., 1999). Possibly, the diffuse white matter lesion and its associated reduction in the cortical grey matter are the neural substrates for the cognitive and motor deficits so often encountered in pre-terms at school age (Taylor et al., 1998; Peterson et al., 2000; Braceywell and Marlow, 2002). In this respect it is interesting to note that about 70% of 209 pre-term infants born <34 weeks who had been admitted to the neonatal intensive care unit of the University Medical Center Groningen in the years 2003–2005 exhibited abnormal GMs at ‘fidgety’ age (47% mildly abnormal GMs and 25% definitely abnormal GMs; unpublished data, see also Blauw-Hospers et al., 2007), whereas the prevalence of abnormal GMs at fidgety age in the general population is about 28% (25% mildly abnormal GMs, <4% definitely abnormal GMs; Bouwstra et al., 2003, in preparation; Hornstra et al., 2003). Other pieces of
evidence that abnormal GMs might be related to periventricular white matter pathology can be derived from previously published studies. First, re-analysis of the detailed data of the study of Ferrari et al. (1990) on brain lesions and quality of GMs in pre-term infants revealed that the presence of substantial ventricular dilatation, which might be regarded as a sign of diffuse periventricular white matter damage (Volpe, 2003, 2005), showed a strong correlation with the presence of definitely abnormal GMs at ‘fidgety’ age and neurological outcome (Table 3). The study of Prechtl et al. (1993) on asphyxia in full-term infants, quality of GMs, and neurological outcome did not allow for such a re-analysis as the large majority of infants had diffuse damage of the nervous system. But the study of Guzetta et al. (2003) on 11 term infants with neonatal cerebral infarction did allow for further analysis. The data indicated that the presence of definitely abnormal GMs around 3 months and the development of hemiplegic CP was related in particular to the presence of lesions of the internal capsule, a major white matter fibre tract affected in periventricular white matter injury (Fisher: p = 0.02), less to abnormalities of the basal ganglia (Fisher: p = 0.06) and not to the degree to which the neocortex was damaged. The data of the Ferrari et al. (1990) and Guzetta et al. (2003) studies do support the idea that abnormal GMs are related to periventricular white matter pathology, i.e. to damage of the efferent connections of the subplate. Whether injury to subplate neurons itself contributes to the generation of abnormal GMs is not clear. However, the high vulnerability of subplate neurons to hypoxia–ischaemia at pre-term age (McQuillen et al., 2003; McQuillen and Ferriero, 2005) suggests that direct subplate damage may play an additional role in the generation of abnormal GMs. The notion that the quality of GMs is related in particular to neurodevelopmental events occurring prior to term age, i.e. during the period when the subplate is supposed to mediate major part of foetal behaviour and when the subplate shows striking developmental changes, is also supported by our studies on the effects of LCPUFA during pre- and early postnatal life. LCPUFA are major components of brain tissue and essential for adequate functioning of the developing brain (Lauritzen et al., 2001). Our studies indicated that prenatal LCPUFA status has a larger effect on the quality of GMs at 3 months post-term than LCPUFA status after term age (Bouwstra et al., 2003a, 2006; Hadders-Algra et al., 2007).

Table 3

<table>
<thead>
<tr>
<th>Ventricular dilatationa</th>
<th>Quality of fidgety GMsab</th>
<th>N</th>
<th>Outcome &gt; 12 months</th>
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<tbody>
<tr>
<td></td>
<td>CP</td>
<td>No CPc</td>
<td></td>
</tr>
<tr>
<td>No/to a minor extent</td>
<td>Normal</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Abnormal</td>
<td>6</td>
<td>3</td>
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<tr>
<td>Substantial</td>
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<td>1</td>
</tr>
<tr>
<td></td>
<td>Abnormal</td>
<td>14</td>
<td>14</td>
</tr>
</tbody>
</table>

abRelation between degree of ventricular dilatation and quality of ‘fidgety’ GMs: Fisher exact test, p < 0.01.

bFrom the description of the movements it is clear that the abnormal movements of the Ferrari et al. study can be classified as definitely abnormal movements according to Hadders-Algra et al. (2004). Normal movements are movements which are not definitely abnormal. In two of the 29 study infants no information was available on movement quality at ‘fidgety’ age.

cCP: presence of spastic diplegia, spastic hemiplegia, or quadriplegia; children who were classified as ‘no CP’ either had no neurological signs, or a monoplegia, minor neurological dysfunction, or a developmental delay at 12–24 months corrected age.

4. Concluding remarks

The assessment of the quality of GMs has become one of the clinical tools to evaluate the integrity of the young nervous system. In the present paper the hypothesis has been advanced that the hallmark of human GM motility, i.e. movement complexity and variation, is generated by the cortical subplate and that abnormal GMs are the result of damage or dysfunction of the subplate and its motor efferent connections in the periventricular white matter. The correctness of the last part of the hypothesis may be tested by studies in which novel imaging techniques such as diffusion-tensor MRI are combined with the assessment of GMs. The notion that the quality of GMs is based in particular on the integrity of the subplate and its connections may also shed light on the type of developmental problems which might be related to abnormal GMs, especially those occurring around 3 months post-term. Abnormal GMs will be related to those forms of CP which are the result of brain lesions involving the periventricular white matter, such as major part of bilateral and unilateral spastic CP and dyskinetic CP (Einspieler et al., 2002). Unilateral spastic CP may, however, also be caused by a more superficially located focal cortical lesion (Cioni et al., 1999); it is conceivable that such a lesion will not present itself in the form of abnormal GMs. If abnormal GMs reflect periventricular pathology, it may be surmised that they may be especially an early marker of dysfunctions requiring complex cortical–subcortical circuitries, such as impairments in the performance of complex motor tasks and executive dysfunction. These suggestions may be explored in future research.

References


