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EVOLUTION IN UNDERSTANDING OF NORMAL AND DEVIANT MOTOR DEVELOPMENT

During the last century knowledge of the mechanisms governing the functions of the central nervous system (CNS) has rapidly increased. This expansion in knowledge was brought about by the development of sophisticated physiologic, 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 behavior is largely controlled by reflex mechanisms[1,2] 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.[3] For instance, nowadays it is assumed that motor control of rhythmic movements such as locomotion, respiration, sucking, and mastication is based on 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. 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 brainstem, is controlled from supraspinal areas via descending motor pathways.[3] The supraspinal activity itself is also organized in networks, large-scale ones, in which cortical areas are functionally connected through direct recursive interaction or through intermediary cortical or subcortical (striatal and cerebellar) structures.[4,5]

The conceptual changes in motor control have been paralleled by changes in ideas on motor development and neurologic assessment of young children. Development is no longer considered to be the result of a gradual unfolding of predetermined patterns in the CNS[6] or of increasing cortical control over so-called lower reflexes.[7] It is currently viewed as a complex process in which genetically based and environmentally driven process continuously interact.[8,9] In particular, the ideas of Edelman,[10,11] the neuronal group selection theory (NGST), proved to be helpful in gaining understanding of the mechanisms directing motor development and developmental motor disorders, such as cerebral palsy (CP).

According to NGST, normal motor development is characterized by two phases of variability.[9] The variation is not random, but is determined by criteria set by genetic information. Development starts with the phase of primary variability, during which variation in motor behavior is not geared to external conditions. Next, the phase of secondary variability takes over, during which motor performance can be adapted to specific situations. Adaptation occurs on the basis of selection guided by afferent information resulting from self-generated motor activity. The transition from primary to secondary variability occurs at function-specific ages. In terms of NGST, children with pre- or perinatally acquired lesions of the brain resulting in CP suffer from stereotyped motor behavior produced by a limited repertoire of primary cortical–subcortical networks.[12] In addition, these children have problems in selecting the most efficient neuronal activity due to deficits in the processing of sensory information.

The idea that spontaneous activity is a fundamental characteristic of neural tissue also affected the way in

which young children are assessed neurologically. Traditionally, the neurologic assessment focused on muscle tone and reflexes,[7] but gradually people started to devote more attention to the observation of spontaneous behavior.[13] Heinz Prechtl was among the pioneers promoting the value of the evaluation of the quality of spontaneous motility during early human development.[14] He discovered that the quality of spontaneous movements of the fetus and young infant (i.e., the quality of general movements) may provide information on the integrity of the young nervous system.

TYPICAL DEVELOPMENT OF GENERAL MOVEMENTS DURING PRE- AND POSTNATAL LIFE

General movements (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.[15] Remarkably, GMs are among the first movements that the human fetus develops, and they emerge prior to isolated limb movements.[16] GMs can already be observed before the completion of the spinal reflex arc, which is accomplished at 8 weeks' postmenstrual age (PMA).[17] This means that GMs, like other motor behaviors produced by CPG networks, can be generated in the absence of afferent information. This underscores the spontaneous or autogenic nature of the first movements[18] and refutes the long-held belief that all movements of the fetus and newborn are reflex in character.[19]

GM development from a phylogenetic perspective

Movements resembling human GMs can be observed in other species, albeit only during prenatal life. For instance, Coghill[20] described GM-like movements in the embryos of the amphibian *Amblystoma*. During the early phases of development, *Amblystoma* exhibits 'total behavior patterns' in which trunk and fore- and hindlimbs participate.

Early motor behavior has been studied especially in the embryonic chick. The basic motility type of the chick embryo is type I motility, which consists of spontaneous, seemingly uncoordinated movements.[21] During type I motility, all parts of the body can move in any conceivable combination.[22,23] Type I motility disappears when the embryo approaches hatching age, to be absent after hatching.

In mammalian fetuses (rat,[24] rabbit,[25] and guinea pig[25]), comparable generalized motility can be recognized. In the fetal rat, generalized motility emerges 1 day after the onset of fetal motility, which starts at embryonic day 15.[24,26] A slight difference between the generalized movements of the rat fetus and those of the chick embryo has been observed. The movements of the rat are in general smoother than those of the chick.[23] After birth, rats no longer show GM-like movements. Instead, they show motility aiming at progression, i.e., weak crawling movements[27] or swimming behavior.[28] Unfortunately, no detailed reports exist on the various forms of prenatal motility in monkeys. But, like other animals, monkeys do not have GM-like movements after birth.[29] In fact, the human newborn seems to be the only newborn creature in which generalized movements persist after birth. Possibly, the human newborn can afford this type of non-goal directed motor behavior, which is especially displayed in the vulnerable supine position due to the presence of sophisticated parental care.[30]

Of course, one could query whether the prenatal general movements of the human fetus are identical to those of the chick and rat embryos. The basic description of generalized motility in various species is the same, and includes the notion that generalized movements are movements in which all parts of the body participate in a very variable way. The observation that all parts of the body participate resulted in the term 'total' or 'mass' movements (in rat[24] and human[7]), and only recently has the term 'general movements' been introduced for spontaneous movements in human preterms.[31] The very variable nature in which the various body parts are coordinated led to the descriptions 'impulsive' (various species),[25] 'seemingly uncoordinated' (chick),[23] and 'uncoordinated' (human),[31,32] and more recently to the description 'coordinated' movement pattern (human).[14] In all studies reported, generalized motility precedes the emergence of isolated limb movements. Thus, the basic features of generalized motility are shared by all hitherto studied subjects. Still, a qualitative difference seems to be present between the generalized movements of the chick and those of the human fetus and infant. The movements of the chick are described as monotonous and lacking rotatory components,[23] whereas complexity and rich variation in movement trajectory, including rotatory movements, are the

hallmark of normal human GMs.[14,33] It is conceivable that the rich variety and complexity of human GMs reflect the seemingly aimless and explorative activity of the primary cortical–subcortical networks on the extensive CPG networks of the GMs in the spinal cord and brainstem. This hypothesis is supported by the finding that human GMs that lack complexity and variation (i.e., GMs that are definitely abnormal) are strong indicators of the development of CP.[33,34]

Ontogeny of GMs in the human

After their emergence during early fetal life, GMs continue to be present throughout pregnancy. The incidence of GMs first rapidly increases between 8 and 10 weeks' PMA,[35] after which it is relatively stable to decrease again after 28–32 weeks' PMA. The latter decrease has been observed in utero[36] and in preterm infants.[31] It should, however, be stressed that throughout pre- and postnatal life, the incidence of GMs is characterized by a large intra- and interindividual variation.[35–38]

GMs show age-specific characteristics (Table 25.1). Little is known about the qualitative changes of GMs during the first 2 trimesters of pregnancy. During the 3rd trimester, GMs are characterized by a large variation and complexity. The movements – described as 'preterm' GMs[39] – 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 'preterm' GMs change into the slower and more forceful 'writhing' GMs, in which the trunk participates less obviously than during the previous GM phase.[39] The 'writhing' GMs constitute a temporary form of GMs, as they disappear around 6–8 weeks' post-term age.[40] Electromyograph (EMG) recordings of GMs[39,41] and H-reflex studies[42] indicated that the periterm period (i.e., the period from 36–38 weeks' PMA until 6–8 weeks' post-term age) is characterized by a temporary increased excitability of the motoneurons. This might explain why the motor behavior around term age was previously described as the phase of 'physiologic hypertonia'.[7] At the end of the 2nd month post term, the 'writhing' GMs are replaced by the final form of GMs, the so-called 'fidgety' GMs. The latter consist of a continuous stream of tiny, elegant movements occurring irregularly all over the body.[40] The transition from 'writhing' to 'fidgety' GMs occurs in general between 6 and 8 weeks' post-term age – thus in a relatively narrow time window. The finding that this change in GM form is more closely related to postmenstrual age than to postnatal age suggests that the transition for a major part is based on endogenous maturational processes.[40] Postnatal experience plays a minor role, as healthy preterm infants in general exhibit their 'fidgety' GMs only 1 week earlier than full-term babies do.[38] Surface EMG recordings indicated that the change from 'writhing' GMs to '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[41] suggested that the EMG changes might point to developmental changes of neuronal membranes throughout the nervous system, changes in muscle innervation (a regression of polyneural muscle innervation),[43] changes in the spinal circuitries (an increasing effect of Renshaw inhibition), and – last but not least – changes in supraspinal organization.

Table 25.1 Age-specific characteristics of normal GMs[39,40]

GM type	Period of presence (weeks PMA)	Description
Preterm GMs	From ± 28 weeks until 36–38 weeks	Extremely variable movements, including many pelvic tilts and trunk movements
'Writhing' GMs	From 36–38 weeks until 46–52 weeks	The variable movements take on a more forceful ('writhing') character. In comparison with preterm GMs, 'writhing' GMs seem to be somewhat slower and to show less participation of the pelvis and trunk
'Fidgety' GMs	From 46–52 weeks until 54–58 weeks	Basic motility consists of a continuous flow of small and elegant movements occurring irregularly all over the body – i.e., head, trunk, and limbs participate to a similar extent. The small movements can be superimposed on large and fast movements

At any GM age, the basic characteristics of normal GMs are (1) participation of all body parts and (2) movement complexity and variation

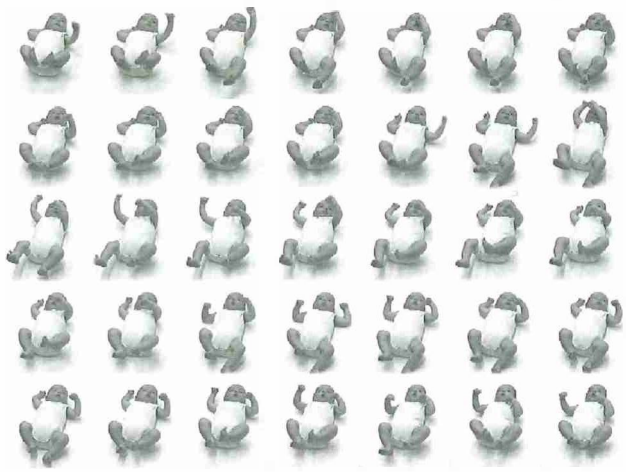
The latter idea is supported by imaging studies indicating that around the age of 3 months post term, functional activity in the cerebellum, the basal ganglia, and the parietal, temporal, and occipital cortices increases significantly.[44]

The 'fidgety' GMs disappear around 4 months post term.[40] They are gradually replaced by goal-directed movements. In terms of neural networks, the gradual change from GM activity into goal-directed behavior could mean that the widely distributed (sub)cortical networks controlling GM activity are flexibly rearranged by means of changed synaptic connectivity into multiple smaller networks.[45] In other words, the large (sub)cortical GM network is cut into various smaller networks. These smaller (sub)cortical networks form the primary neuronal repertoires for the control of specific motor behaviors, such as goal-directed motility of the arms and the legs, and postural control. Due to the dissolution of the primary neuronal network of the GMs, the development of GMs does not include a transition from a primary neuronal repertoire to a secondary repertoire. This underscores the unique position of GMs in human motor development, and supports the notion that the (sub)cortical networks involved in the control of GM activity form the neural building blocks for later motor skills.[9]

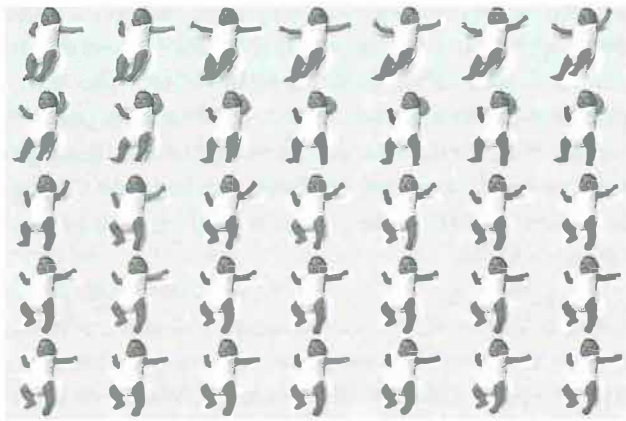
ABNORMAL GMs

Characteristics of abnormal GMs

Keywords describing the quality of GMs are variation and complexity (Figure 25.1).[14,33,39,46,47] Complexity points to the spatial variation of the movements. Complex movements are movements during which the infant actively produces frequent changes in direction of the participating body parts. The changes in movement direction are brought about by continuously varying combinations of flexion–extension, abduction–adduction, and endorotation–exorotation of the participating joints. GM variation represents the temporal variation of the movements. It means that, across time, the infant produces continuously new movement patterns. Thus, the primary parameters of GM quality evaluate two aspects of movement variation. This fits with 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.[9,12]



(A)



(B)

Figure 25.1 Representation of video frames with GMs of two infants at the 'fidgety' GM age. The video recording starts in the left hand upper corner and should be read like the lines in a book. The interval between the video frames is 0.24 seconds. The infant in (A) was born at term and shows normal fidgety GMs. The continuously varying positions of the limbs illustrate the rich spatial and temporal variation of normal movements. The infant in (B) was born at 28 weeks' PMA. She shows definitely abnormal GMs. The abnormal character of the movement is reflected by the lack of variation, indicated by the virtually identical frames, which induce the false impression that the infant hardly moves. (The video recordings were made in collaboration with the Department of Developmental and Experimental Clinical Psychology, Faculty of Psychological and Social Sciences; figure published with permission of the parents and the Nederlands Tijdschrift voor Geneeskunde[48])

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 25.2). Normal–optimal GMs are abundantly variable

Table 25.2 Classification of the quality of GMs[47]

Classification	Complexity[a]	Variation[a]	Fluency[b]
Normal–optimal GMs	+++	+++	+
Normal–suboptimal GMs	++	++	–
Mildly abnormal GMs	+	+	–
Definitely abnormal GMs	–	–	–

[a]Complexity and variation: +++, abundantly present; ++, sufficiently present; +, present, but insufficiently; –, virtually absent or absent
[b]Fluency (the least important aspect of GM assessment): +, present; –, absent

and complex. In addition, they are also fluent. Normal–optimal movements are relatively rare: only 10–20% of 3-month-old term infants show GMs of such a beautiful quality.[49,50] The majority of infants shows 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.[39,51] 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 that can be considered as pathologic. Their presence points to a loss of supraspinal control.[52] 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 that 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.[53]

VALIDITY OF ABNORMAL GMs

Various pre-, peri-, and neonatal adversities, such as maternal diabetes, intrauterine growth retardation, preterm birth, perinatal asphyxia, neonatal hyperbilirubinemia, and neonatal treatment with dexamethasone, can give rise to abnormal GMs.[54] Definitely abnormal GMs are specifically but not exclusively related to discernible lesions of the brain.[39,51,55,56] Children with Down syndrome often show mildly abnormal GMs.[57] It has also been demonstrated that movement quality is not a fixed phenomenon. It can change in various ways: movement quality can be transiently affected by illness,[58] and movement abnormalities can vanish or become more distinct with increasing age. The majority of changes in GM quality occurs 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).[47,59] Within the three GM phases (Table 25.1), movement quality is relatively stable (Figure 25.2).

The predictive validity of GM quality varies with the age at which the GMs are evaluated and with the type of outcome (Figure 25.2). The best prediction can be obtained by longitudinal series of GM assessments. Infants who persistently show definitely abnormal GMs, even while passing the transformational phases at

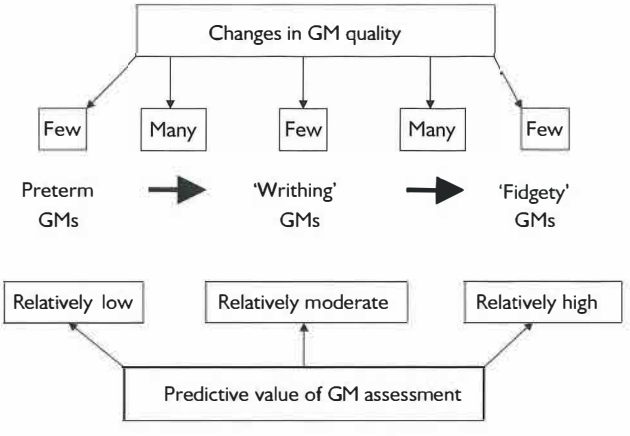


Figure 25.2 Schematic diagram indicating that GM quality is relatively stable within a specific GM phase, but changes frequently during the periods of transition (indicated by the bold arrows). Due to the frequent changes in quality, GM assessment prior to term age has relatively low predictive value

36–38 weeks' PMA and 6–8 weeks post term, have a high risk (70–85%) for the development of CP.[51,55] Infants who persistently show cramped–synchronized GMs invariably develop CP.[60] 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 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, predict CP with an accuracy of 85–98%.[34,47,59] Recent studies indicate that infants with definitely abnormal GMs at 'fidgety' age who do not develop CP usually show other developmental problems, such as minor neurologic dysfunction (MND), attention-deficit hyperactivity disorder (ADHD), or cognitive problems.[47,59] Mildly abnormal GMs at 'fidgety' age are related to the development of MND, in particular with respect to coordination problems and fine manipulative disability, ADHD, and aggressive behavior,[47,53,59] but the accuracy of prediction of 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 neurologic examination.[47]

TECHNIQUE AND RELIABILITY OF GM ASSESSMENT

The assessment of the quality of GMs focuses on the amount of movement variation and complexity exhibited by the infant (Figure 25.1). These parameters can be appreciated by means of Gestalt perception of the observer.[14] 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 behavior of specific body parts (e.g., fisting). GM evaluation also includes the evaluation of movement fluency (Table 25.2). But this is the least important aspect of the assessment. Regrettably, our visual system has an innate sensitivity to spot a loss of movement fluency, and this visual propensity for the detection of abnormalities in movement fluency (e.g., jerkiness, tremulousness, and stiffness) interferes to some extent with the assessment of the major components of the GMs (i.e., movement complexity and variation).

The evaluation of movement complexity and variation is demanding and requires offline assessment by means of a video recording. Assessment of the movements in 'real life' introduces errors and should be avoided.[50] Ideally, about 5–10 minutes of real-time motility is recorded with the infant in an adequate behavioral state. The absolute minimum duration of a GM video is 3 minutes with real-time behavior. Only this minimum duration allows for an evaluation of the overall variation in the infant's motor repertoire. The video has the advantage that it also offers the opportunity of movement replay at high speed, which facilitates the evaluation of movement complexity and variation. A high-speed replay produces an effect that is comparable to the effect produced by the video-frame sampling procedure of Figure 25.1.

GMs are affected by the behavioral state of the infant.[61] The optimal state for GM analysis is active wakefulness (i.e., Prechtl's state 4).[62] In this state, the splendid variation and fluency of normal GMs is expressed best. During other behavioral states, normal GMs have features reminiscent of abnormality, implying that a non-optimal state interferes with movement classification. The effects of behavioral state on normal GMs are summarized in Table 25.3. Practically, this means that GMs are preferably assessed in state 4. When a video recording only contains GMs during state 2 (or state-2-like conditions), the primary parameters of GM analysis – complexity and variation – can still be evaluated. GMs should not be assessed during crying or non-nutritive sucking, including thumb sucking.[61]

The basic principles of GM assessment can be learned in 2 days. Thereafter, it requires further practice of about 100 GM recordings to become a skilled observer.[50] Various studies reported that the intra- and inter-observer agreement of GM assessment of skilled observers is high (κ-values around 0.80, implying an excellent inter-rater and intra-rater reliability).[53,59]

Table 25.3 Effect of behavioral state on normal GMs[61]

Behavioral state[a]	Complexity and variation	Fluency
2: active sleep or REM sleep	Normal	Reduced
4: actively awake	Normal	Normal
5: crying	Reduced	Reduced
NNS[b]	Reduced	Normal

[a]Behavioral states (numbers according to Prechtl[62]) are only fully established from 36–38 weeks' PMA onwards[63]
[b]Non-nutritive sucking

CONCLUDING REMARKS

Assessment of the quality of GMs is a sensitive tool to evaluate brain function in the fetus and young infant. Currently, the application of GM assessment in the fetus is technically highly demanding: adequate assessment implies evaluation of the motor behavior of virtually all parts of the body for a period of at least 3 minutes. Most likely, future sonography machines and dedicated software programs will allow GM assessment in the fetus.

GMs have a function complementary to the traditional neurologic examination. Prediction of developmental outcome on the basis of longitudinal series of GM assessment is best. Second best is prediction on the basis of an assessment at 'fidgety' age (i.e. at 2–4 months post term). Prediction of developmental outcome on the basis of GM quality prior to term age is, however, relatively poor.

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