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ORIGINAL ARTICLE

Development of corticospinal motor excitability and cortical silent period from mid-childhood to adulthood — a navigated TMS study

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Summary
Objectives. — We characterized the maturation of the excitability of the motor cortex and corticospinal tract from childhood to adulthood using electric field (EF) navigated TMS and correlated the results with manual dexterity.
Methods. — Both hemispheres of healthy right-handed children (6—9 years, $n = 10$), preadolescents (10—12 years, $n = 13$), adolescents (14—17 years, $n = 12$) and young adults (22—34 years, $n = 12$) of both genders were examined. The optimal cortical representation site and resting motor threshold (rMT) were determined for the abductor pollicis brevis muscle. Motor-evoked potential (MEP) latencies and amplitudes in relaxed and active states, input-output curves and silent period (SP) durations were determined. Manual dexterity was assessed with the Box and Block Test.
Results. — rMT (in terms of maximal stimulator output or EF strength) decreased with age ($P < 0.001$) and stabilized when reaching adolescence. The MEP amplitude ($P = 0.037$) and latency

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increased ($P < 0.001$) with age. Input-output curves showed age-dependent changes in several parameters. SP duration decreased with age ($P < 0.001$), and demonstrated hemispheric asymmetry in the children ($P = 0.030$). Manual dexterity correlated negatively with rMT ($P < 0.001$). *Discussion.* — The excitation/inhibition balance develops with age and correlates with manual dexterity. Strong corticospinal inhibition was observed in the children and this was found to decrease with age. Interhemispheric asymmetry was only observed for SP duration in the children. Knowledge of normal development is crucial for the understanding of developmental disabilities and using estimates of effective EF may be advantageous in future pediatric studies.

Introduction

Neuromotor function plays an essential role in normal cognitive development and is frequently impaired in children with developmental disabilities. Fine motor skills appear in a rudimentary fashion during the first year of life. Noticeable gains are then made through the early school years and there is continued improvement in quality and speed of motor skills until adolescence or even until the age of 30 years [17]. The status of motor function may act as a 'biomarker' for neighboring systems and circuits, which are responsible for the behavioral anomalies in developmental disabilities [13,61].

Neuroimaging studies of central nervous system (CNS) development have demonstrated age-related increases in white matter that are thought to reflect progressive myelination, whereas age-related decreases in grey matter are thought to reflect both synaptic pruning and myelination [21]. The maturation of the corpus callosum continues into young adulthood, but the growth of callosal regions containing motor fibers may be already complete before the age of 10 years [7]. Myelination of the corticospinal tract is completed morphologically by early childhood [79]. Neuromotor development and its pathological functional changes can be readily examined with transcranial magnetic stimulation (TMS) [43]. The motor threshold (MT) that reflects the developmental stage of myelination of the corticospinal tracts is high in children and then decreases approximately linearly until mid-adolescence [16,17,48] or even until early adulthood [51]. It is also known that the motor-evoked potential (MEP) amplitudes are smaller and even polyphasic in early childhood and the motor conduction velocities are slower in children compared with adults, mainly attributed to immature myelination [43,48]. The central motor conduction time gradually shortens from 2 to about 13 years and then plateaus [16,48]. The conduction time in peripheral components also initially decreases, but then from the age of 5 years progressively increases in proportion to the height [16] jointly resulting in the progressive prolongation of MEP latency. However, the height-adjusted MEP latency (suggested to parallel the complex rearrangement of the corticospinal tract during acquisition of complex motor capabilities) decreases, whereas the latency during muscle contraction increases with age. This difference, called the latency jump, has been suggested as a specific TMS-derived indicator of maturation [8]. Late muscular MEP responses involving reticulospinal tract are more prevalent in the proximal than distal muscles, and suggested to be of diagnostic value in children for detection of unilateral dysfunction of the CNS [38,42].

With TMS, it is also possible to assess inhibitory functioning and its deviations during neuromotor development. This information cannot be obtained with any other neuroimaging methodologies [29]. Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the CNS and has a central role in a wide variety of physiological and biochemical processes such as regulation of cognition [45], memory and learning [27], circadian rhythms [1], neural development [60], adult neurogenesis [52], and motor function [23] including motor learning [75]. GABA has an elementary and homeostatic, possibly also compensatory role for intrinsic motor excitability [22]. $GABA_B$ has been suggested to have a more important role than $GABA_A$ for motor functioning [73] and its dysfunction may be important in behavioral anomalies in developmental disabilities such as autism spectrum disorders [15,53,58], complex motor stereotypies [26], in evaluating the cortical excitability in mild traumatic brain injury [71], epilepsy [6,56], and Tourette's syndrome [57]. Understanding the role of $GABA_B$ in motor plasticity could have clinical relevance in terms of therapeutic rehabilitation [18,24,59].

Paired-pulse paradigms assess corticospinal inhibition reflecting $GABA_A$ and $GABA_B$ activity and $GABA_B$ neurotransmitter activity can be assessed by silent period (SP) measurements [31,82]. In children, results from early paired-pulse studies have suggested that there is less net intracortical inhibition through $GABA_A$ receptor activity [37,83]. However, this was questioned in a recent study, which individually took into account the contaminating effect of concurrent facilitation that instead was enhanced in young children [69]. The maturational trajectories of TMS-evoked inhibitory parameters reflecting especially $GABA_B$ activity have been poorly defined for (SP) or lacking for long-interval cortical inhibition, LICI. Previous studies on maturation using SP measurements have shown somewhat contradictory results, with either no age-related changes [20,28], or an increase in duration with age [41]. Furthermore, transcallosal excitability/inhibition can be evaluated by other useful TMS parameters such as ipsilateral SP and paired-pulse interhemispheric inhibition (IHI) that have been recently characterized during development [10] and may be related with motor performance [20]. These may