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Altered transcallosal inhibition evidenced by transcranial magnetic stimulation highlights neurophysiological consequences of premature birth in early adulthood

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ABSTRACT

Background and objective: A very preterm birth can induce deleterious neurophysiological consequences beyond childhood; alterations of the corpus callosum (CC) are reported in adolescents born very preterm along with cognitive impairments. The question remains whether neurophysiological alterations are still detectable in adulthood such as an alteration in CC inhibitory function. The aim of the present study was thus to examine transcallosal inhibition in young adults born very preterm compared to counterparts born at term.
Study participants & methods: Transcallosal inhibition was probed by measuring the ipsilateral silent period (iSP) using transcranial magnetic stimulation (TMS) in 13 young adults born at 33w of gestation or less (20 ± 3. 2y) and 12 young adults born at term (22 ± 1. 75y). Single high-intensity TMS were delivered to the primary motor cortex (M1) ipsilateral to the preactivated first dorsal interosseous (FDI) muscle. Occurrence, latency, and duration of iSP were measured in the FDI EMG activity, for both hemispheres alternatively (10–12 trials each) along with their resting motor threshold (RMT).
Results: In individuals born very preterm as compared to individuals born at term, ISP occurred less frequently ($p < .0001$), its latency was longer ($p = .004$), especially in the non-dominant hemisphere, its duration shorter ($p < .0001$), and RMT was higher in the non-dominant M1 than in the dominant.
Conclusions: Impairment of transcallosal inhibition along with asymmetry of M1 excitability in young adults born very preterm as compared to those born at term underline that neurophysiological consequences of a preterm birth can still be detected in early adulthood.

1. Introduction

Preterm birth can have long-term deleterious consequences on function in childhood [30, 33]. Motor, cognitive and learning impairments are found in up to 50% of children born very prematurely (before 32 weeks of gestation or GA) even if they are not presenting cerebral palsy, brain lesion or trauma and are considered as having a typical development [43]. Neuroimaging studies have identified potential neural correlates to these functional impairments such as structural alterations that are even detected in late adolescence [9, 29]. For example, diffusion tensor imaging (DTI to study tractography) has shown microstructural abnormalities and alterations of neural connectivity in adolescents born preterm as compared to term counterparts [48]. Studies combining DTI and neurodevelopmental measures (for example verbal and performance IQ, visual-motor integration) have found that reductions in volume of brain structures engaged in cognitive functions as well as microstructural alterations of white matter (WM injury, also called encephalopathy of prematurity) at 12 years of age are related to lower clinical performance [8, 22]. The third trimester of gestation is a critical period for pruning of axonal fibers,

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myelination, and establishment of synaptic connections [10, 20]. A premature birth occurring during this critical moment is deemed to have deleterious consequences on white matter development, thus explaining WM injury [34, 53, 55]. Recent studies of cellular and molecular mechanisms have identified late oligodendrocyte progenitors as failing to fully mature and susceptible to ischemic death during the critical period of development of neural circuitry interrupted by the preterm birth [3]. Corpus callosum (CC) has been repeatedly identified as a key structure undergoing WM injury; more precisely its thinning has been targeted as a consequence of a preterm birth [36, 37].

The CC is the largest bundle of myelinated nerve fibers in the entire nervous system and a functionally relevant WM structure [25]. With an estimated 200 million axons connecting homologous cortical areas, it serves both inhibitory and excitatory reciprocal influences between hemispheres that balance hemispheric activity for most functions, including motor, cognitive and psychological functions [4, 25]. Many studies have supported an association between a preterm birth and a reduced CC thickness in childhood [21, 50–52], adolescence [14] and even in early adulthood [1, 11, 49]. More precisely, the severity of CC alterations was related to age of birth; the earlier born the more affected the CC, even in infants without periventricular WM injury or necrosis, i.e. without apparent white matter lesions [16].

Transcranial magnetic stimulation (TMS) of the primary motor cortex (M1) is a painless transient and powerful electromagnetic field able to activate brain cells through the scalp. Figure-eight TMS coils allow for a focal stimulation of muscle representations in M1. It is a useful tool for non-invasively investigating cortical motor physiology and the development of the motor systems, including callosal motor function. At intensities beyond the motor threshold, single-pulse TMS produces a motor evoked potential (MEP, in muscles contralateral to M1 cells beneath the coil) that is measurable by means of surface electromyography (EMG) and informs on M1 excitability. To our knowledge, only five studies used TMS to test corticomotor aspects of development in individuals born preterm ([13, 39], [44, 45]). Flamand et al. [13] have been the first authors to show that children born very preterm (< 32 weeks GA) presented with lower corticomotor excitability than counterparts born at term. This study also showed that corticomotor excitability was related to GA and to motor skills at 8 years of age. In other words, the longer the gestation the higher was M1 excitability (i.e., the lower the motor threshold measured with TMS) and the higher were the scores on clinical tests of motor performance [13]. Pitcher et al. [39] showed similar main findings in a larger cohort of children born very preterm.

Moreover, Schneider et al. [44] have been the first authors to use the ipsilateral silent period (iSP: EMG silence in preactivated muscle due to TMS of ipsilateral M1) as an indicator of transcallosal inhibitory dysfunction in adolescents born very preterm. They denoted that the three principal parameters of the iSP were altered, i.e. that iSP was less frequent (decreased occurrence), that its latency was longer (lengthened interhemispheric transfer time) and that iSP was of shorter duration (less efficient transcallosal inhibition) than in counterparts born at term. Pitcher et al. [38] further reported evidence of a reduced potential for M1 plasticity in adolescents born preterm as compared to counterparts born at term. Precisely, they used low-frequency repetitive TMS to decrease M1 excitability and showed that adolescents born preterm presented with a reduction of downregulating effects (namely less long-term depression of M1 excitability as tested by TMS). M1 excitability was also shown to be positively correlated with gestational age in adolescents [45] as previously detected in children [13, 39]. Importantly, the higher excitability of M1 circuits was associated to better scores on cognitive measures [45].

In early adulthood, preterm birth has been associated to sustained cognitive impairments [5, 12]. The only reports of possible underlying neural substrates have been neuroanatomical differences from counterparts born at term [26]. TMS has not yet been used to investigate whether differences in the neurophysiology of motor systems could underlie these cognitive differences at that stage. Given the CC issues denoted in children [36, 37] and adolescents [44], and given the CC primary role in cognition [6, 31, 32], it is expected that callosal dysfunction could still be present in young adults born very preterm and be a possible explanation of cognitive impairments reported in the literature. The primary aim of the present study was to examine the activity of transcallosal inhibitory pathways in young adults born very preterm as compared to their counterparts born at term. We hypothesized that, as a by-product of preterm birth's deleterious impact on WM development, transcallosal inhibition tested by measuring the iSP using TMS would be impaired in this population.

2. Material and methods

2.1. Participants

Twenty-five young right-handed adults aged 17–25 years old participated in the study. The group of individuals born very preterm (n = 13, 8 women, 20 yrs. ± 3.2 yrs., GA = 29 weeks ± 3.5 weeks i.e. ≤ 33 wGA) was compared to a group of individuals born at term (n = 12, 8 women, 22 yrs. ± 1.75 yrs., GA ≥ 37 wGA, birth weight ≥ 2500 g) without any history of developmental delay or abnormal sensorimotor or cognitive development. Inclusion criteria common to both groups were being 17–25 years of age and currently enrolled in a pre-university college program or having already completed a pre-university college degree. Exclusion criteria were birth defects or genetic abnormalities detected during pregnancy or before discharge from the hospital, neonatal complications (grade 3–4 intraventricular hemorrhage, cyst originating from severe ischemia in the periventricular white matter, oxygenation until 36 weeks corrected age), intellectual disability (IQ < 70), attention deficit hyperactivity disorder (either being diagnosed with ADHD or taking medication for hyperactivity or lack of attention), major cognitive disorders, and any contraindication to TMS testing as found in safety guidelines (Rossi et al. 2009: brain surgery, tumor or infection; history of seizure or concussion; implanted devices such as pacemakers, pumps, metal in skull or jaw; cerebral palsy; stroke; medication affecting neural excitability; or pregnancy). All participants or one of their parents (for participants aged 17 years old) signed a written informed consent detailing the experimental procedures and approved by the local Institutional Review Boards.

2.2. EMG recordings

Participants were comfortably seated in an adjustable chair with their upper extremities relaxed on arm supports. EMG activity was recorded from the first dorsal interosseous muscles (FDI) bilaterally using surface Ag–AgCl electrodes (Kendall MediTrace 200 Series: My Well Care, Concord, ONT, Canada) placed in a standard monopolar configuration (electrodes on FDI belly and proximal phalanx of index finger) with a ground electrode on the ulnar styloid process (Biometrics-NexGen amplifiers, Gwent, UK). EMG signals were bandpass-filtered (20–450 Hz), amplified before digitization (2 kHz) and computer-stored for online display and offline analysis (PowerLab acquisition system; LabChart, ADInstruments, Colorado Springs, CO, US).

2.3. TMS testing

Monophasic TMS was applied over the FDI representation in M1 with a figure-of-eight coil (70-mm diameter; Magstim Company Limited, Whitland, UK) connected to a Magstim 200^2 stimulator. The coil orientation induced a postero-anterior current within M1. The “hotspot” in each hemisphere was identified as the coil location at which TMS elicited the largest MEP in the contralateral FDI at the lowest intensity. The hotspot was marked on the scalp with a surgical pen to ensure reliable coil positioning throughout the experiment. The following procedures were strictly replicated for the two hands, always