Motor nerve conduction velocity and somatosensory evoked potentials in the newborn and young child in relation to thyroid function
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Chapter 3

Somatosensory evoked potentials in the newborn and young child. A literature review
Introduction

In recent years, the use of somatosensory evoked potentials (SEPs) in the newborn and young child, obtained by electrical stimulation of the median nerve at the wrist, has received increased attention. In several reviews the anatomy and development of the pathways involved in the generation of SEPs, the methodology of recording SEPs, and the clinical applications for SEP recording, are described. This chapter focuses on short latency median nerve SEPs as well as other aspects relevant to this thesis.

Anatomy and development of the SEP pathways

In the generation of median nerve SEPs mainly proprioceptive afferent fibers of muscle spindles. These are the thickest and fastest conducting myelinated fibers. Afferent impulses through the median nerve travel along the brachial plexus, dorsal root, posterior column of the cervical spinal cord, cuneate nucleus and after crossing the midline along the medial lemniscus and thalamus to reach the contralateral postcentral parietal cortex (Fig. 1a). The first synaptation is located in the cuneate nucleus at the spinomedullar junction and the second in the ventroposterolateral nucleus of the thalamus. From here impulses are relayed to the postcentral sensory cortex. The development of the SEP pathways starts in the 6th postmenstrual week. Maturation proceeds sequentially from peripheral nerve to cortex. Myelination is the last step in maturation. In the peripheral nerve, it occurs in a somatofugal manner from the cell bodies towards the fiber endings. Myelination within the nervous system starts before birth and continues mostly after birth. This process also continues in case of preterm birth. However, at term, preterm infants show a delay in central myelinisation in comparison to fullterm infants shortly after birth.

Methodology

At first, nomenclature and methodological details regarding median nerve SEPs in the newborn and young child differed between authors. In recent years, however, considerable agreement has been reached. The technical development of an advanced mobile multichannel evoked potential machine has improved utilization of recording SEPs outside as well as inside the neonatal intensive care unit. Infants generally tolerate the use of SEPs well. Preferably, a low number (25-50) of 0.5 Hz electrical stimuli of 0.1 - 0.2 ms duration are delivered using a hand-held device which is placed on the median nerve at the wrist. An intensity sufficient to evoke a visible abductor pollicis brevis muscle contraction is
Fig. 1a. Schematic representation of the median nerve SEP pathways from peripheral nerve to cortex.

(FC=Fasciculus cuneatus, ML=Medial lemniscus, NclC=Nucleus cuneatus, PSC=Primary somesthetic cortex, VPLThncl=Ventral posterior lateral thalamic nucleus)

Fig. 1b. Schematic representation of recording cortical SEPs by electrical stimulation of the median nerve at the wrist (● active electrode, ○ reference electrode, ◇ ground electrode)
applied. Skin temperature should be guaranteed to be above 36° C. Silver-silver chloride disk electrodes (diameter 10 mm) are used. The negative electrode is placed over the contralateral postcentral region for the upper extremities, i.e. two cm posterior to C3/C4 (C3'/C4') according to the international 10 - 20 electrode system. The reference electrode is placed in midfrontal position (Fz) and the ground electrode is placed on the lower arm (Fig. 1b). The skin-electrode resistance is preferably below 2 kΩ. To increase signal-to-noise ratio, SEPs are recorded with a low bandpass filter (2-100 Hz). An analysis time of 200 msec is sufficient to observe short latency SEPs. The first negative peak 'N1' (Fig. 2) reflects the first cortical potential at the contralateral postcentral sensory cortex or more precisely, a single tangentially oriented dipole located in area 3b of the post-central gyrus. SEP recordings should be duplicated to test reproducibility. By using an AC filter (50 Hz) artefacts caused by the patient monitoring and support equipment can be reduced. The correct placement of stimulator or electrodes may be limited by the presence of intravenous lines.

An unstable clinical condition, especially in the neonatal period, may result in a poor quality SEP recording or may cause the recording to be interrupted. The success rate of performing median nerve SEPs depends on gestational age and clinical condition and ranges from 65 % to 100 %.

**Clinical applications**

The N1 peak latency of the cortical SEP of the median nerve reflects the functional integrity and maturational state of impulse conduction along the myelinated fibres of the peripheral and central somatosensory pathways. From the literature reference values of median nerve SEP latencies for term and preterm infants will be presented and SEP features will be discussed in intrauterine growth retardation, prenatal exposure to betamethasone/TRH, asphyxia, adaptation to extrauterine life,
behavioral state, medication, cranial ultrasound abnormalities, hyperbilirubinemia and hypothyroidism.

Reference values of median nerve SEP latencies
Many authors have contributed towards establishing reference values of median nerve SEP latencies in the newborn and young child (Table 1). Reference values are strongly dependent on the methodology employed and have therefore changed over the years. Only studies published over the last decade are reviewed here.

Reference values of median nerve SEP latencies for term infants
Laureau et al.\(^\text{15}\) described a longitudinal study of 18 healthy term infants. Median nerve SEPs were performed in the first week of life and repeated at 2, 3 and 6 - 7 months of age. In this study 512 stimuli in a frequency of 4 Hz were given. A high filter bandpass (30 - 3000 Hz) was used. Newborns were tested when drowsy or asleep, while older infants were tested during wakefulness. Because of low cortical SEP amplitudes, in 85% of the newborns a cortical median nerve SEP could be recorded. Taylor and Fagan.\(^\text{16}\) presented reference values of median nerve SEPs in patients aged 4 months to 35 years. They show that mean N\(_1\) peak latency decreases with age until the age of 2-3 years and then increases again with age up to adulthood. They stimulated the median nerve with 256 stimuli in a frequency of 4.1 Hz and used a high filter band pass (30 - 3000 Hz). In this study small groups of 11 to 19 young children are included in groups spanning 4 - 6 months of age. This limits the use of these data. Bongers -Schokking et al.\(^\text{9}\) studied 35 healthy term infants during the first week of life. They advocate a low number of 25 to 50 stimuli and a low filter bandpass (1-100 Hz) while paying attention to the arousal state of the infant. Laureau and Marlot\(^\text{17}\) reported on a study performed in 41 healthy term infants. They demonstrate the use of cortical and spinal SEPs after stimulating of median as well as tibial nerves. Majnemer et al.\(^\text{18}\) compared median nerve SEPs and BAEPs in 19 healthy term infants (gestational age: 37 - 42 wk) tested during the first week of life and in nine preterm infants (gestational age: 32 - 36 wk) tested around 40 weeks PMA (39 - 42 wk). N\(_1\) peak latencies are similar for both groups. The infants were tested while drowsy or asleep. No effect of gestational age on SEPs was found. They used the same methods as mentioned earlier for this group of investigators.\(^\text{15}\) George and Taylor\(^\text{19}\) reported reference values in a group of 23 healthy term infants with a mean gestational age of 39.9 ± 1.2 (SD) weeks. The children were recruited from hospital personnel and friends of the authors. The method used
### Table 1. Median nerve (short latency) SEPs in the newborn and young child: reference values and methodology

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>GA (wk)</th>
<th>age</th>
<th>n</th>
<th>N&lt;sub&gt;t&lt;/sub&gt; (ms)</th>
<th>stimuli (s&lt;sup&gt;−1&lt;/sup&gt;)</th>
<th>filter (Hz)</th>
<th>success (%)</th>
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<tr>
<td>Laureau et al, 1988&lt;sup&gt;15&lt;/sup&gt;</td>
<td>18</td>
<td>37-42</td>
<td>&lt; 1w</td>
<td>29</td>
<td>25.0 ± 2.9</td>
<td>512</td>
<td>4</td>
<td>30-3000</td>
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<td></td>
<td></td>
<td>2m</td>
<td>14</td>
<td>20.4 ± 1.2</td>
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<td></td>
<td></td>
<td>3m</td>
<td>16</td>
<td>19.2 ± 1.1</td>
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<td></td>
<td></td>
<td>6-7m</td>
<td>28</td>
<td>17.5 ± 0.8</td>
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<tr>
<td>Taylor and Fagan, 1988&lt;sup&gt;16&lt;/sup&gt;</td>
<td>136</td>
<td>-</td>
<td>4-8m</td>
<td>19</td>
<td>17.7 ± 0.9</td>
<td>256</td>
<td>4.1</td>
<td>30-3000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9-15m</td>
<td>14</td>
<td>15.7 ± 0.9</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>16-22m</td>
<td>11</td>
<td>15.4 ± 0.6</td>
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<tr>
<td>Klimach and Cooke, 1988&lt;sup&gt;10&lt;/sup&gt;</td>
<td>102</td>
<td>26-41</td>
<td>&gt; 1w</td>
<td>-</td>
<td>162-3.05xPMA</td>
<td>100</td>
<td>0.5</td>
<td>2-100</td>
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<td>Bongers et al, 1989&lt;sup&gt;9&lt;/sup&gt;</td>
<td>35</td>
<td>37</td>
<td>&lt; 1w</td>
<td>35</td>
<td>28.7 ± 2.9</td>
<td>25-350</td>
<td>0.5</td>
<td>1-100</td>
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<td>41</td>
<td>36-42</td>
<td>0-2w</td>
<td>21</td>
<td>26.7 ± 5.7</td>
<td>500</td>
<td>2.5</td>
<td>20-2000</td>
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<td>19</td>
<td>37-42</td>
<td>&lt; 1w</td>
<td>31</td>
<td>24.6 ± 3.1</td>
<td>512</td>
<td>4</td>
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<td>9</td>
<td>32-36</td>
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<td>24.8 ± 2.2</td>
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<td>37-42</td>
<td>0-2w</td>
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<td>21.8 ± 3.1</td>
<td></td>
<td></td>
<td>30-3000</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>7-13w</td>
<td>17</td>
<td>20.7 ± 2.5</td>
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<td>Gibson et al, 1992&lt;sup&gt;20&lt;/sup&gt;</td>
<td>40</td>
<td>37-42</td>
<td>-</td>
<td>38</td>
<td>30.1 ± 6.8</td>
<td>256-1024</td>
<td>1.5</td>
<td>10-3000</td>
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<tr>
<td>Karninsky et al, 1992&lt;sup&gt;11&lt;/sup&gt;</td>
<td>53</td>
<td>28-40</td>
<td>&gt; 3w</td>
<td>-</td>
<td>-</td>
<td>168-3.44xPMA</td>
<td>0.9-1.7</td>
<td>1-100</td>
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<tr>
<td>Taylor et al, 1996&lt;sup&gt;12&lt;/sup&gt;</td>
<td>22</td>
<td>26-32</td>
<td>27-28w</td>
<td>14</td>
<td>114.4 ± 18.8</td>
<td>25-40</td>
<td>0.5</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>29-30w</td>
<td>22</td>
<td>90.6 ± 19.6</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>31-32w</td>
<td>10</td>
<td>70.8 ± 11.9</td>
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</table>

GA = gestational age, m = months, PMA = postmenstrual age (weeks), w = weeks

differed from their earlier study in older children. It consisted of 64 stimuli in a frequency of 1.1 Hz and 2 filter bandpasses from 5 to 1500 Hz and 30 to 3000 Hz. Their success rate was 100%. Mean values were calculated for 3 age groups. Gibson et al.<sup>20</sup> also studied healthy term infants (n=40), but used 256 to 1024 stimuli and high filter bandpass. The large variability of their results is explained by the wide range of postmenstrual age and inclusion of less mature cortical wave forms in their study.
Reference values for preterm infants

Klimach and Cooke\textsuperscript{10} were the first to include a large group of 102 preterm infants (gestational age: 26.7 - 40.4 wk PMA, age at SEP: 27.7 - 41.1 wk PMA). They were tested in a stable condition (no mechanical ventilation or \textsubscript{O}_2 support) as soon as possible after birth during natural sleep. The authors present a linear relation between N\textsubscript{1} peak latency and PMA with a decrease of 3 ms per week. In fact, only three infants born at less than 30 weeks contribute to the data presented. Karnisky et al.\textsuperscript{11} reported on a longitudinal study in healthy term and preterm infants from 31 to 40 weeks PMA. They express their findings in a linear regression formula for N\textsubscript{1} peak latency regarding PMA similar to the one by Klimach and Cooke.\textsuperscript{10} Taylor et al.\textsuperscript{12} presented a study on median nerve SEPs in 22 very preterm infants (gestational age: 27 - 32 wk). Infants were studied only if they were clinically healthy, suffered no ultrasound abnormalities and had a normal neurological status during follow up (6 - 25 months). Twenty-five to 40 stimuli were given with a frequency of 0.5 Hz and a low filter bandpass (1 - 100 Hz). Behavioral state during SEP recording is not mentioned. They report a 100 % success rate and established reference values for 3 age groups, using repeated SEPs (46 recordings: 1x [n=2], 2x [n=16], 3x [n=4]). The N\textsubscript{1} peak latencies found, form a continuum with those reported earlier in the literature.

Intrauterine growth retardation

In infants with intrauterine growth retardation a delayed myelination caused by insufficient nutrition or an accelerated maturation induced by intrauterine stress, could be expected. Only a few studies have examined the relation between SEPs and low birth weight or, more specifically, intrauterine growth retardation. Bongers-Schokking et al.\textsuperscript{21} studied a group of 44 term infants with a mean gestational age of 40.0 ± 1.4 (SD) weeks and a mean birth weight of 3311 ± 402 (SD) gram. SEP investigation was carried out during the first week of life. Qualitatively, they find higher amplitudes and better defined peaks as birth weight increases. Quantitatively, they find a shorter N\textsubscript{1} peak ascending time with increasing birth weight. Pierrat et al.\textsuperscript{22} studied a group of 56 preterm infants with a mean gestational age of 31 ± 1.4 (SD) weeks and mean birth weight of 855 ± 35 (SD) gram. SEP investigation was carried out after the end of the second week of life. No significant correlation between severity of intrauterine growth retardation and delay of SEPs was found.
Prenatal exposure to betamethasone/TRH
De Zegher et al.\(^2\) described a prospective, controlled, but not strictly randomized study in 26 infants (gestational age: 29 - 36 wk). They find that prenatal exposure to betamethasone / TRH accelerates SEP-assessed neural maturation followed by a compensatory, relative deceleration during the early neonatal period.

Asphyxia
De Vries et al.\(^2\) were the first to compare median nerve SEP latencies with clinical assessment and cranial ultrasound findings in 34 term infants with birth asphyxia. They find that SEPs are especially useful for identifying infants at risk of a poor neurodevelopmental outcome in infants with moderate encephalopathy and in those who showed transient increased periventricular echogenicity on cranial ultrasound. Gibson et al.\(^2\) also found a close correlation between neurologic outcome and SEP latencies in a group of 30 asphyxiated term infants. The infants with normal SEPs by 4 days of age were all found to be neurodevelopmentally normal on follow up at 1 year. None of the infants with abnormal SEPs after 4 days had a normal outcome. Taylor et al.\(^2\), who studied 57 term infants with perinatal asphyxia, measured VEPs in addition to SEPs. They confirm the usefulness of both methods. In 1993, in an excellent review on SEPs in term infants with postasphyxial encephalopathy, de Vries described the largest study group so far consisting of 73 infants.\(^2\) She finds that SEPs are already predictive for neurodevelopmental outcome if performed within 24 hours after births. Sensitivity and specificity increase to 89.4 % and 86.6 %, respectively on day 3, and 94.4 % and 91.6 % before discharge. Harbord and Weston\(^2\) compared median nerve SEPs and EEGs and preferred the first to predict short term neurologic outcome at 9 - 36 months in a group of nine term newborn infants (age: 1 - 7 wk) with perinatal asphyxia. Majnemer and Rosenblat\(^2\) reported the only study performed in preterm infants. They find that median nerve SEPs measured in a group of 78 high-risk newborn infants with birth weights below 1501 gram or the 3rd percentile or asphyxia, accurately predict neurodevelopmental status at school entry. Recently, Scalais et al.\(^3\) published a study of 40 term asphyxiated newborns in whom multimodality evoked potentials (flash VEPs, SEPs, BAEPs) were measured during the first week of life. Latencies of both flash VEPs and median nerve SEPs correlate significantly with early Sarnat stage and neurological outcome at 24 months corrected age.
Adaptation to extrauterine life

An interesting observation was done by Pierrat et al. They find a marked decrease in $N_1$ peak latency during the first week of life in a group of eight low risk preterm infants (gestational age: 34 - 36 wk). Only during the second week of life values similar to cross-sectional data were found. To explain this finding several factors were considered such as a difference in $P_{O_2}$ tension before and after delivery, a change in neurotransmitters and improvement of synaptic efficiency.

Behavioral state

Desmedt and Manil were the first to describe SEPs in infants during waking, during rapid eye movement sleep (REMS) and during slow wave sleep (SWS). In a study of 34 healthy term infants during the first week of life, $N_1$ peak latency are similar during waking and REMS but increase significantly in SWS. Willis performed SEPs in 16 healthy infants between 2 and 12 months of age in order to study the influence of SWS. He reported lower amplitudes as well as longer latencies in SWS as compared to wakefulness. Bongers-Schokking confirms the influence of arousal state on SEPs and describes prolonged latencies during SWS as compared to REMS in a group of 13 term infants.

Medication

An extensive overview of cerebral evoked potentials during psychopharmacologic treatment in adults was published by Saletu. This work demonstrates that drug induced short latency changes do not reach statistical significance. In a study by Borah and Matheshwari concerning a group of 45 diagnosed cases of epilepsy (11 - 54 years), no effect of antiepileptic drugs, including phenobarbitone, on short latency SEPs is found. For a group of seven comatose patients, Ganes and Lundar reported a full suppression of all spontaneous EEG activity by a thiopentone infusion without any effect on SEPs.

Cranial ultrasound abnormalities

When Klimach and Cooke presented their reference values of SEPs in preterm infants, they also presented a study in 30 preterm infants with ultrasound abnormalities of the brain (mean gestational age: 30.5 wk, mean age at first SEP: 35.3 wk PMA). They find a correlation between SEPs and neurologic outcome, especially the SEP recordings performed near 40 weeks postmenstrual age. However, patient selection was unclear; five infants were lost or excluded from follow up, the
follow-up period was short (6 - 16 months), and follow-up data were not systematically collected. Willis et al.\textsuperscript{38} describe 47 preterm infants with periventricular hemorrhage (birth weight < 1500 g, age at the time of SEPs recording: 2, 4 and 6 months corrected age, age at follow-up: 22 months corrected age). All infants with a single recording of SEPs with a unilaterally abnormal (> 3 SD) or absent N\textsubscript{1}, proved abnormal at follow-up (n = 12). De Vries et al.\textsuperscript{39} studied SEPs in nine infants with rapidly progressive ventricular dilatation (5 preterm and 4 term infants, 3 of whom suffered a lumbosacral myelomeningocele). They note an increase in $N_1$ peak latency during a period of rapidly progressive ventricular dilatation, followed by a decrease after shunt insertion or spontaneous stabilisation of ventricular growth. The decrease in $N_1$ peak latency after shunt insertion seemed to be related to the cerebrospinal fluid pressure shortly before shunting. In a prospective study of 126 preterm infants (mean gestational age: 30.2 wk) De Vries et al.\textsuperscript{40} stated that cranial ultrasound is a more sensitive method than SEPs to predict neurodevelopmental outcome. Pierrat et al.\textsuperscript{41} who studied 33 infants with severe periventricular leucomalacia (gestational age: 26 - 41 wk) demonstrated that SEPs performed between 31 and 49 weeks PMA do not provide reliable information about neurodevelopmental outcome, especially in those infants with cystic lesions restricted to the periventricular white matter. Recently, Pierrat et al.\textsuperscript{42} compared SEPs following posterior tibial nerve and median nerve stimulation in 39 preterm infants with a mean gestational age of 29.5 ± 0.5 (SD) weeks, as well as cranial ultrasound. Posterior tibial nerve SEPs have a better predictive value than median nerve SEPs. However, cranial ultrasound is best for predicting cerebral palsy. Ekert et al.\textsuperscript{43} once again advocate the use of median nerve SEPs during the first three weeks of life, especially in those preterm infants with a high risk cranial ultrasound (periventricular echodensities). Normal SEPs predict a normal outcome with respect to cerebral palsy.

**Hyperbilirubinemia**

Bongers-Schokking et al.\textsuperscript{44} studied 59 term infants, grouped according to their highest serum bilirubin levels during the first week of life. SEPs were recorded on the day of the highest bilirubin level, 2-3 days later and at five weeks. At all three measurement, they find $N_1$ peak latencies to be prolonged in the group of infants with the highest serum bilirubin levels (> 250 mmol/l) compared to the group of infants with lower serum bilirubin levels, and to normal controls.
Hypothyroidism
After two small studies by Laureau and Norcross, more extensive studies were performed by Bongers-Schokking et al. on the clinical application of SEPs in infants with primary congenital hypothyroidism (CHT). They demonstrated that SEPs performed in 27 infants with CHT before or within 1 week after initiation of therapy, reveal a maturational delay in N peak latency (among several SEP parameters) compared to 103 healthy controls. A longitudinal study of a group of 29 infants with CHT, in whom SEPs were recorded six to seven times during the first year of life, N peak latencies remained prolonged.

Conclusions
In recent years, the use of median nerve SEPs in the newborn and young child has received increased attention. In studies regarding reference values for term and preterm infants, patient selection and other methodological issues such as number and rate of stimuli, use of high or low filter bandpass and behavioral state of the infant during SEP recording, are recognized to be of great importance. Cortical N peak latency in median nerve SEPs may be increased by asphyxia, intracranial abnormalities, hyperbilirubinemia and congenital hypothyroidism. In asphyxiated term infants, median nerve SEPs may be a useful prognostic test to predict later neurodevelopmental outcome. Measuring cortical N peak latency in median nerve SEPs may be used when studying the effect of thyroid function on the developing nervous system.

References


