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High frequency oscillations after median nerve stimulations in healthy children and adolescents

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ABSTRACT

The aim of the present research was to address somatosensory high frequency oscillations (400–800 Hz) in healthy children and adolescents in comparison with healthy adults. We recorded somatosensory evoked potentials following median nerve stimulation in nineteen resting healthy children/adolescents and in nineteen resting healthy adults with eyes closed. We administered six consecutive stimulation blocks (500 sweeps each). The presynaptic component of high frequency oscillations amplitudes was smaller in healthy children/adolescents than in healthy adults (no difference between groups was found as far as the postsynaptic component was concerned). Healthy children/adolescents had smaller presynaptic component than the postsynaptic one (the postsynaptic component amplitude was 145% of the presynaptic one), while healthy adults showed the opposite (reduction of the postsynaptic component to 80% of the presynaptic one). No habituation phenomena concerning high frequency oscillation amplitudes were registered in neither healthy children/adolescents nor healthy adults. These findings suggest that healthy children/adolescents present with significantly different pattern of somatosensory high frequency oscillations compared with healthy adults' ones. This different pattern is reasonably expression of higher cortical excitability of the developing brain cortex.

1. Introduction

Electrical stimulation of the upper limb evokes, along with the low-frequency somatosensory evoked potentials (LF-SEP), also oscillatory activity in the high-frequency range (400 Hz to 800 Hz) so called high-frequency oscillations (hereafter, HFOs). These are more evident on the frontal-parietal regions controlateral to the stimulated arm. In the last 15 years, somatosensory HFOs presented increasing interest as they show strict relationship with arousal. In fact, HFOs' amplitude decreases during sleep (Halboni et al., 2000) and increases by the opening of the eyes (Gobbelé et al., 2000; Restuccia et al., 2004), contrary to the LF-SEPs' amplitudes that do not change under these conditions. These findings suggested HFOs to represent a "somatosensory arousal system" (Halboni et al., 2000; Gobbelé et al., 2000). Moreover, HFOs evoked by lower limb stimulation do not change their amplitude during quiet stance, contrary to LF-SEPs' ones that are significantly reduced (Restuccia et al., 2008). Further, HFOs' amplitudes do not undergo habituation (Restuccia et al., 2011). These evidences suggest HFOs' generators to play a general role in modulating somatosensory inputs related to rapid environmental changes.

However, the unique perspective of arousal might be insufficient to fully understanding the neurophysiological meaning of somatosensory HFOs. In fact, somatosensory HFOs represent a neurophysiological marker of a cortical-thalamic bi-directional system that modulates somatosensory input to the cortex (Restuccia and Della Marca, 2015). The more this system works properly (the corresponding neurophysiological marker is represented by HFOs of higher amplitudes), the more the cortex receives phasic somatosensory input, and, eventually, the better is the somatosensory input processed. The experimental evidence suggesting this interpretation of somatosensory HFOs comes from several different papers: Restuccia and Coppola (2015) demonstrated that auditory stimulation enhances somatosensory HFOs (cross-sensory sensitization), and Götz et al. (2015) showed how somatosensory evoked responses are modulated by the overall information context (HFOs, the hallmark of this modulating system, change accordingly to the task-at-hand).

This interpretation of somatosensory HFOs settles the potential interest for a developmental perspective. It is known that the very early stages of somatosensory processing reach an adult-like pattern very soon (around 2 years of age) (Pihko et al., 2009). However, it is extremely plausible that maturational gradients of the cortex can modify somatosensory HFOs responses across childhood/adolescence.

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To the best of our knowledge, only one paper by Nakano and Hashimoto (2000) explicitly addressed this issue. These authors compared low- and high-frequency somatosensory responses, following median nerve stimulation, between two groups of healthy subjects: children (6–12 years old) and young adults (19–32 years old). Authors found that children presented with generalized and overall larger both low- and high-frequency somatosensory responses: larger N20 and P27 amplitude and larger N20 and P27 duration (in agreement with previous findings (Tanosaki et al., 1999)), but also larger HFOs amplitude and duration (total HFO responses, pre-synaptic/early component HFOs – from the HFOs' onset to the N20 peak –, and post-synaptic/late component of HFOs – from the N20 peak to the HFOs' endpoint). It is worth recalling that Nakano and Hashimoto (2000) registered somatosensory responses in opened eyes subjects. This point will be discussed thoroughly later on. Unfortunately, authors did not spend much time in trying explaining the physiology of these findings.

In a recent experiment addressing N13 and N20 habituation and recovery cycle in healthy children/adolescents compared with healthy adults (Zanini et al., 2016) we found no group difference as far as the N20 amplitude was concerned and we found clear-cut absence of N20 habituation across stimulation trials in children/adolescents and two to three times shortened recovery cycle on each interstimulus interval (5, 10, and 20 ms) in the same group compared with the adult one. These findings suggested cortical hyper-excitability/responsiveness in healthy children/adolescents compared with healthy adults.

Therefore, the disagreeing findings concerning larger N20 amplitude in children/adolescents than in adults, between Tanosaki et al.'s (1999), Nakano and Hashimoto's (2000) studies and our recent paper (Zanini et al., 2016) suggested us to extend to the same group of healthy children/adolescents and healthy adults that we included in the habituation and recovery cycle study, a somatosensory HFOs study. In fact, cortical hyper-excitability/responsiveness in children/adolescent might very likely impact on HFOs, and larger HFOs in children/adolescents still deserves physiological explanation.

2. Materials and methods

2.1. Participants

We enrolled 19 (10 males) healthy developing children/adolescents (mean age 9 years and 11 months, age range 5–15 years) whose parents signed written informed consent. Absence of any neurological or psychiatric disorder was certain, on the basis of a parents' interview. We also enrolled 19 (8 males) healthy adults (mean age 36 years and 6 months, age range 27–51 years) who signed written informed consent. They were selected among employees of Scientific Institute Eugenio Medea, of the Udine University Hospital, or of the Catholic University of the Sacred Heart in Rome, Italy, for whom absence of any neurological or psychiatric disorder was certain, on the basis of a direct interview. Children/adolescent and adults were not relatives. All participants were those enrolled for our previous study (Zanini et al., 2016). The research project was approved by the Ethical Committee of the Scientific Institute Eugenio Medea.

2.2. Neurophysiological recordings

SEP recording was performed using a commercially available five-channel Medelec™ Synergy apparatus (Viasys Health Care). We administered electrical stimulation to the right-median nerve at the wrist using a constant current square wave pulse (0.2 ms width, cathode proximal) and a stimulus intensity set just above the motor threshold (approximately in a range between 4 and 8 mA). Six consecutive series of 500 sweeps were collected and averaged at a repetition rate of 5 Hz. Active electrodes were placed over the contralateral parietal area (P3) referenced to F3; on the sixth cervical spinous process (Cv6), referenced to an electrode located immediately above the thyroid cartilage (anterior cervical (AC)); in the supraclavicular fossa (Erb's point), referenced to Fz. Subjects were asked to lie with eyes closed on a couch in a warm and half-lit room. Since high-frequency SEPs are largely influenced by drowsiness or sleep (Halboni et al., 2000) participants were asked to signal the occurrence of drowsiness, to temporarily stop the examination. However, this maneuver was never necessary. The analysis time was 50 ms, with a sampling rate of 20000 Hz. The amplifier bandpass was 10–30000 Hz (12 dB roll-off). An automatic artefact-rejection system excluded from the average all runs containing transients exceeding ± 65 μV at any recording channel. To ensure baseline stabilization, SEPs were filtered off-line by means of a digital filter within a bandpass of 3–3000 Hz. One may suspect that HFOs can result, at least in part, from a filter artifact. However, it is not uncommon to find, in some subject with quite high-amplitude HFOs, clear oscillations on the ascending slope of the N20 response in wide bandpass traces. Moreover, HFOs are typically absent in the 30–40 ms latency range, while wide bandpass SEPs usually shows large deflections at the same latencies. Both findings should exclude, in principle, that HFO are merely due to a filtering artifact (Fig. 1).

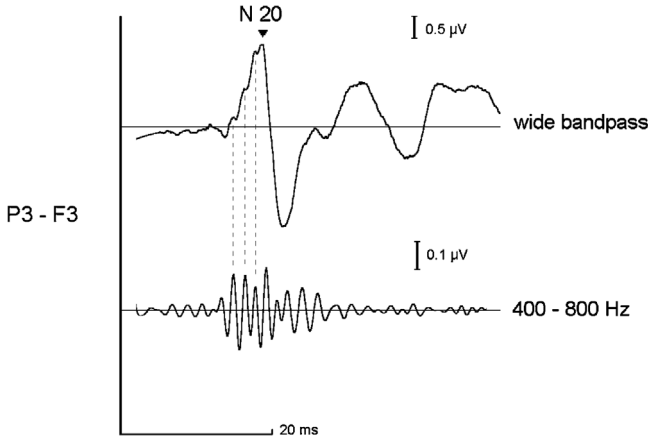

Fig. 1. Wide bandpass and filtered traces in adult.
SEPs obtained from one healthy adult. P3-to-F3 recordings. Top: wide bandpass traces. Bottom: narrow bandpass (400–800 Hz) traces. In this subject, HFO components, coincident in time with high-frequency wavelets in filtered traces, are clearly recognizable on the ascending slope of the N20 potential in unfiltered traces. Moreover, no high-frequency signal is recognizable on filtered traces, in correspondence of slow potentials following the N20 response. This should exclude that HFOs could merely be the result of a filter artefact.

2.3. Statistical analysis

We first analyzed latency and amplitude of the LF-SEPs. We measured latency and amplitude of the primary N20 response on the P3-to-F3 traces, of the spinal N13 response on the Cv6-to-AC traces and of the Erb's point response on the Erb-to-Fz traces. The amplitude of the Erb's point response was evaluated from the first positive peak to the negative peak; that of the spinal N13 was evaluated from the baseline; and that of the N20 amplitude was evaluated as peak amplitude from the baseline. For the present paper, no further analyses were done on LF-SEP components as they were out of our main interest and already described (Zanini et al., 2016).

P3-to-F3 traces underwent time-frequency analysis (continuous wavelet transformation (CWT); Morlet's wavelet family) by means of an automated signal analysis software (Autosignal version 1.7). This allowed to recognize, within the 400–800 Hz window, two separate components with slightly different frequencies, the former centered on the rising slope of the LF N20, and the latter beginning just prior to the N20 peak and reaching its maxima in the N20 descending slope. Thus, each trace was digitally filtered with a bandpass of 400–800 Hz and then analyzed. As far as the evaluation of the HFO amplitude on the P3-to-F3 trace was concerned, instead of fixing pre-established intervals,