Research paper

Stimulus artifact removal to detect trigeminal sensory evoked potentials

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A B S T R A C T

Objective: Large stimulus and myogenic artifacts usually prevent detection of sensory evoked potentials to electrical stimulation in trigeminal sensory territory (t-SEP). Stimulus Artifact (SA) removal can be obtained by means of two stimulating modes (Dual Mode Stimulation - DMS) having in common a fixed cathode alternatingly referred to opposed anodes, resulting in SAs of opposite polarity. Opposite SAs progressively cancel each other out during averaging, without interaction with the underlying bio-electrical events.

Methods: Using DMS, dermatomal t-SEP were recorded from C5/C6 scalp sites in 24 healthy volunteers after selective, electrical stimulation of five trigeminal nerve areas: supraorbital, infraorbital, superior alveolar, inferior alveolar and auriculotemporal.

Results: Reproducible t-SEPs were obtained after stimulation at all sites and showed the classical W shape, without significant differences related to the stimulated area. Cortical responses were formed by a sequence of individual peaks labelled, according to polarity and mean latency, as P8, N13, P19, N27, P38. A later, less stable component followed (N55-P67), poorly defined or absent in about one third of subjects.

Conclusions: The described technique represents a novel approach, within reach of any neurophysiological unit, to record dermatomal SEPs to electrical stimulation of several, discrete areas of significant clinical interest, covering the whole trigeminal sensory territory.

Significance: DMS represents a simple and robust tool to remove SA as the main drawback that has so far prevented recording of t-SEPs in daily clinical practice.

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1. Introduction

A reliable, shared methodology, within reach of any neurophysiological unit, to detect somatosensory evoked potentials to non-invasive, electrical stimulation of trigeminal sensory territory (t-SEP) is not yet available.

Two main reasons explain this persistent failure. First, the proximity between the stimulating and recording sites induces large stimulus artifacts (SA) with a long tail masking most of cortical waveform. Moreover, a stimulus strength such as that needed to percutaneous activation of a trigeminal branch is likely to induce both direct and reflex myogenic artifacts which, detected as far field potentials, may disguise a cortical t-SEP. So far, these serious limitations have been overcome only by direct, bipolar stimulation of individual trigeminal branches at their respective foramina (Leandri et al., 1985; Cruccu et al., 1987; Leandri et al., 1989). However, this approach, although effective in assessing peripheral and subcortical tracts of trigeminal pathway, is invasive and shows the drawback of an almost total failure to display consistent cortical responses (Jones, 1993).

This daunting perspective makes electrical stimulation of trigeminal districts a kind of electrophysiological minefield. All these pitfalls have been avoided only by using sophisticated methodologies such as air-puff stimulation, which a priori removes the side effects of electrical stimulation (Hashimoto, 1988).

Previous attempts have been made to reduce excessive SA by swapping cathode and anode (Stöhr and Petruch, 1979; Bennett and Jannetta, 1980; Findler and Feinsod, 1982; Salar et al., 1982; Altenmüller et al., 1990). However, this approach, so far limited to stimulation of lower lip, gum and tongue, involving a continuous anatomical change of the active cathode, implies a methodological bias which may explain, as emphasized by Jones (1993), the marked lack of agreement between these studies.

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The purpose of this paper is to describe a procedure of SA removal based on the use of two stimulating modes (Dual Mode Stimulation – DMS) having in common a fixed cathode alternately referred to opposed anodes, resulting in two SAs of similar shape and amplitude but opposite polarity. Opposite SAs progressively cancel each other out during averaging without interaction, if purely additive, with the underlying bio-electrical events. The advantage of this approach is that it can work in several, discrete trigeminal areas, provided that the traditional concept of SEP to stimulation of a peripheral nerve trunk is abandoned in favor of a more functional, dermatomal, approach.

2. Materials and methods

2.1. Subject and patient population

All experiments have been performed on 24 healthy volunteers, 14 females and 10 males, ranging in age between 26 and 75 years, most of them recruited from the nursing and medical staff of ForcANA Clinic after full informed consent and approval of the local ethical committee. Most subjects were studied several times both during the phase of methodological development and later during normative data collection. Two patients with trigeminal diseases were also studied. The first one, suffering from a left trigeminal meningioma, had been treated with stereotactic radiosurgery for over 4 years and showed a painful anaesthesia affecting the maxillary and mandibular trigeminal branches. The second one, with a fully normal neurological examination, had a typical trigeminal neuralgia mainly involving the right maxillary branch.

2.2. The dual mode stimulation (DMS) technique

As shown in detail in Fig. 1, the stimulating device is formed by a central cathode (2 mm) referred to opposing anodes (2 mm), 10 mm apart, inserted in a semi-rigid plastic support (3 x 1 cm). This arrangement provides two different montages and, consequently, two stimulating modes having in common the fixed cathode (C-A1 and C-A2). The first step of the technique concerns the location of the proper skin site and angular position of the stimulating device, allowing a clear-cut polarity inversion of SA by changing the stimulus mode. After starting the averaging process, DMS proceeds with alternating use of the two stimulus modes, guided by a careful visual control of the resulting effects on the artifact until its complete removal (see legend of Figs. 1 and 2).

To facilitate the change of stimulus mode, the opposite anodes had been connected to a bidirectional toggle device. Immediate change of stimulus mode can be obtained by manual switching between the two positions without the need to interrupt stimulation or change its frequency.

Artifact removal is usually obtained by averaging of 100–150 trials and is considered satisfactory when a residual SA of negligible duration and an amplitude not exceeding 1–2 μV is obtained. However, during t-SEP recording, which implies adequate amplification of the signal, DMS must be continued throughout the recording session to avoid SA reappearance.

2.3. DMS methodology in trigeminal territories

For each tested trigeminal area, the choice of the optimal stimulus point was dictated by the need to be as far as possible from the motor points of the nearby facial muscles. Direct myogenic artefacts are unlikely to result from direct stimulation of muscle fibres due to their high threshold; they usually originate from activation of low threshold intramuscular motor nerve endings (Troni et al., 1983).

A prefrontal scalp recording (Fp1-Fz and Fp2-Fz), as shown in Figs. 1, 2, 4, was preferred in the development phase of stimulation...
methodology, as the most suitable site for unambiguous detection of "far field" direct or reflex myogenic artifacts without any confusing interference with a concomitant t-SEP.

2.3.1. **DMS in ophthalmic territory**

For stimulation of the supraorbital nerve (SON) zone (Fig. 2A), the best choice turned out to be placing the stimulus device at the upper edge of the eyebrow with the cathode placed at the middle of the eyebrow arch.

As shown in Fig. 2B, DMS performed with the same parameters subsequently employed in this subject for t-SEP recording, totally removed SA and did not elicit any myogenic artifact. As stimulus intensity increased, clear-cut myogenic artifacts of increasing amplitude were recorded which would have inevitably escaped without SA removal.

2.3.2. **Blink reflex to stimulation in ophthalmic territory**

Since the described methodology for stimulation of SON area seems provocative considering the high risk of inducing reflex activity with stimulation in this region, the blink reflex was deliberately evoked in two subjects, to detect the real risk of interference of reflex artifacts on t-SEP recording (Fig. 3).

In both cases, blink threshold was significantly higher than the stimulus intensity usually employed to evoke t-SEP and as expected, high frequency stimulation (4.7 Hz) dramatically and persistently inhibited the reflex response.

2.3.3. **DMS in maxillary territory**

At least two stimulation sites of potential clinical interest proved to be suitable for DMS in the maxillary territory (Fig. 4, left).

The first one, was the infraorbital nerve (ION) zone. The stimulus device was placed with the cathode corresponding to the intersection between a horizontal line starting at the origin of nasolabial fold and a vertical line corresponding the outer border of iris. The proper angular orientation of the stimulator to induce polarity reversal of SA with DMS was about 45 degrees.

The second one was the territory of the superior alveolar nerve (SAN) following stimulation of the upper gum. For this peculiar stimulus site, the stimulator was arranged on a flexible plastic sheet with the posterior wall fully insulated to limit current spread to the adjacent mucosa and nearby muscles. The stimulator was place on the upper gum with the central cathode corresponding to the junction between the first molar and second premolar. A purpose-made cotton roll helped to maintain the stimulator in place and to part it from the mucosa of superior lip and cheek; moreover, it was further secured by taping cables on the skin of contralateral upper and lower lips. The stimulus intensity was adjusted to induce a slight, always bearable toothache.

2.3.4. **DMS in mandibular territory**

At least two stimulation sites proved to be suitable for DMS in mandibular territory (Fig. 4, right).

The first one was the territory of the inferior alveolar nerve (IAN). Lower gum stimulation was performed using the same approach already described for SAN with the difference that the cathode was placed on the lower gum at the junction between the first molar and the second premolar.

The second one was the cutaneous zone of the auriculotemporal nerve (ATN). The stimulator was placed in an upright position with the central cathode 1.5–2 cm anterior to the tragus.
2.4. Trigeminal SEP recording procedure

Trigeminal SEPs were obtained from 18 subjects of the sample. No more than one SEP modality was recorded in a single recording session. Two SEP modalities were obtained from four subjects in separated recording sessions.

The first step was to define the correct location of DMS device and the proper stimulus intensity being that, usually 3–4 mA, giving no or marginal myogenic artifacts. The latter, when present, were well evident already in the initial phase of averaging. Larger myogenic artifacts were often visible as a slight focal muscle twitching and were well felt by the subject itself. A stimulus duration of 0.05 ms and a sensation of a clear-cut but gentle cutaneous tapping reported by the tested subject were mandatory requirements.

Trigeminal SEPs were recorded after independent and subsequent stimulation of the right and left sides from contralateral and ipsilateral face regions of the primary sensory cortex (C5-Fz and C6-Fz of the International 10–20 system) with a passband of 3 Hz to 3KHz (Cruccu et al., 2008).

A stimulus frequency of 4.7 Hz was used to inhibit any reflex activity, to avoid a repetition rate submultiple of the AC line frequency (50 Hz) as well as to shorten the recording time.

When a suitable cortical response was obtained by averaging 300 to 450 trials, the same procedure was replicated after a rest interval of few minutes, to test t-SEP reproducibility.

In cases of suboptimal signal-to-noise ratio, not so infrequent being t-SEP a dermatomal SEP (see Discussion), the quality of the recorded waveform usually did not improve by continuing the averaging process over 400–500 trials.

In these cases, as exemplified in Fig. 5, a different strategy was adopted. Three to four subsequent blocks of averaged responses, not exceeding 250–300 trials, were first recorded with a rest interval of 2–3 min between them. The Grand Average (GA) of all recorded blocks represented the first assessment. The GA resulting from a subsequent, identical procedure provided the second one. Due to the significant improvement of waveform reproducibility, the double GA procedure has been the prevailing approach to collect normative t-SEP data.

3. Results

3.1. Results in normal subjects

3.1.1. General features

Reproducible t-SEPs were bilaterally obtained in all subjects from all tested trigeminal areas and reported results refer to 44 responses recorded after stimulation of 12 SON, 8 ION, 8 SAN, 8 IAN and 8 ATN areas.

All t-SEPs recorded from contralateral scalp area, showed a quite reproducible waveform, similar for all stimulus sites, in

![Table 1](image)

Mean Latencies and Interside Differences of t-SEP components.

|       | P8    | N13   | P19   | N27   | P38   | N55   | P67   |
|-------|-------|-------|-------|-------|-------|-------|-------|
| Mean latency (ms ± SD) | 8.5 ± 1.1 | 13.2 ± 0.72 | 19.5 ± 1.9 | 27.0 ± 2.0 | 38.2 ± 2.8 | 54.9 ± 3.4 | 67.2 ± 3.8 |
| Interside difference (ms ± SD) | 1.3 ± 1.2 | 0.3 ± 1.1 | 1.0 ± 0.9 | 1.7 ± 0.9 | 2.1 ± 1.3 | 3.3 ± 2.9 | 3.9 ± 3.7 |

![Fig. 6](image)

Fig. 6. Trigeminal SEPs recorded after stimulation of SON zone in 3 normal subjects. Contra- and ipsilateral responses are shown after independent and subsequent stimulation of the right (R) and left (L) side. Legend of labels: P1 (P8), N1 (N13), P1 (P19), N2 (N27), P2 (P38), N3 (N55), P3 (P67). A residual direct myogenic artifact is indicated by asterisk.
agreement with the classic W shape common to most SEPs and were formed by a sequence of waves labelled, as a function of polarity and mean latencies, as P8, N13, P19, N27, P38, N55, P67 (Table 1). Figs. 6–8 show contra- and ipsilateral t-SEP waveforms after independent stimulation of both sides in 9 subjects of the sample well representative of the range of t-SEP morphological features in our normal sample. To allow a more direct comparison with the results of other Authors as well as to achieve an easier reading of figures, the wave sequence, as pointed out in the Legends, was expressed by a simpler labelling (P1, N1, P1, N2, P2, N3, P3).

The occasional presence of direct myogenic artifacts, usually of small amplitude and always occurring within the first 10 ms, never hindered the definition of the cortical response, including the P1-N1 components. This was true even with occasional artifacts of larger amplitude (Fig. 7: C.A., L; Fig. 9: D.M., R). Reflex artifacts were never observed in the expected time interval ranging from 10 to 20 ms. The SA, when present, was always of negligible duration and with an amplitude never exceeding 1.5–2 μV.

3.1.2. Analysis of individual components

No significant difference in latency, amplitude and inter-side variability was observed for all t-SEP components after stimulation at all five sites. This finding is not surprising considering the marginal differences in length between all tested trigeminal pathways. This is even more true for inter-side differences of t-SEP components. Consequently, all data have been pooled together.

The early positivity (P8) showed a mean latency of 8.5 ms ± 1.1 and an occurrence of 80%.

The sequence N13-P19-N27-P38 was the waveform fraction with maximum occurrence and stability having been recorded in all subjects in both sides. As confirmed by mean latency values (ms ± SD), N13 (13.2 ± 0.72) showed the least inter-subject variability, followed by P19 (19.5 ± 1.9), N27 (27 ± 2) and P38 (38.2 ms ± 2.8).

The following N55-P67 component showed the maximum variability and minimum occurrence, being totally absent (Fig. 9: D.M., R and L) or characterized by a poorly defined shape and latency (Fig. 6: M.B., L; Fig. 8: A.S., R) in about one third of t-SEP. In acceptable recordings (29), the mean latency values (ms ± SD) were 54.9 ± 3.4 for N55 and 67.2 ± 3.8 for P67.

Likewise, mean inter-side variability (ms ± SD), except for the early P8 (1.3 ± 1.2), progressively increased for each component as a function of latency, being the least for N13 (0.3 ± 1.1) followed by P19 (1.0 ± 0.9), N27 (1.7 ± 0.9), P38 (2.1 ± 1.3), N55 (3.3 ± 2.9) and P67 (3.9 ± 3.7).

The peak-to-peak mean amplitudes (μV ± SD) were 0.6 ± 3.4 (N1-P1), 1 ± 3.1 (N2-P2) and 0.9 ± 0.5 (N3-P3).

3.1.3. Ipsilateral responses

In most cases, no reproducible responses were recorded from ipsilateral scalp site. In 9 of the 44 recordings (20%) a wave complex of small amplitude with latencies reproducing the contralateral N13-P19-N27 fraction was observed as exemplified in Fig. 7: O.L., R and Fig. 8: M.R., L and F.C., R).

4. Results in patients with trigeminal diseases.

In both cases (Fig. 9) the results were in full agreement with clinical findings, showing the complete absence of the contralateral t-SEP after stimulation of the affected side in the patient with left
Fig. 8. Trigeminal SEPs recorded after stimulation of IAN (7,8) and ATN (9) zones in 3 normal subjects. Contra- and ipsilateral responses are shown after independent and subsequent stimulation of the right (R) and left (L) side. Residual, low amplitude, direct myogenic artifacts are indicated by asterisks. A low amplitude ipsilateral SEPs can be observed in 7 (L) and 9 (R). Legend of labels: P1 (P8), N1 (N13), P1 (P19), N2 (N27), P2 (P38), N3 (N55), P3 (P67).

Fig. 9. Only t-SEPs contralateral to the stimulated side are shown. t-SEP was absent (C6) after stimulation of the left, affected side and fully normal (C5) after stimulation of the right, healthy side in the patient with left trigeminal meningioma (above). Normal t-SEPs, apart from the presence of a myogenic artifact at C5 (*) and the bilateral absence of N3-P3 component, were recorded after subsequent stimulation of both sides in the patient with right Trigeminal Neuralgia and fully normal neurological examination. Note the absence of neurovascular conflict on MRI (below).
meningioma and normal t-SEPs after stimulation of both sides in the patient with trigeminal neuralgia (Crucu et al., 1987).

5. Discussion

Anode rotation around a fixed cathode, used as a pivot, is a well-known strategy to reduce the stimulus artifact in peripheral nerve conduction studies (Kimura, 1989; Caress, 2007). It is probably less well known that this procedure can sometimes identify two different anode positions inducing a polarity reversal of SA rather than its reduction. This finding, not so reproducible in distal limb tracts such as wrist or palm, proved to be very consistent in trigeminal territory, probably due to a more favorable local volume conductor.

The obvious, practical choice was to put in conflict during averaging the two opposite SAs to try to cancel them. However, DMS is legitimated only if the SA proves to be a simple additive artifact, that is, an artifact that masks the underlying bio-electric events without interacting with and distorting them.

That this is the case is demonstrated by the unambiguous emergence, with SA removal, of otherwise hidden local myogenic artifacts strictly occurring, as expected, within the first 10 ms and with the same morphological features of the corresponding “near field” potential.

SA removal provided two main advantages. First, unmasking myogenic artifacts is the necessary premise to remove them by locating the correct stimulus site and properly modulating its intensity. Moreover, it allowed to prove that the much-feared reflex activity was never observed in the expected time range from 10 to 20 ms. This is not surprising considering the low intensity and the high frequency of stimulation that provide a powerful shield against any type of reflex activity.

Since the cathode position is unchanged, depolarization always occurs at the same site. This is supported by the stable site and features of tactile sensation referred by the tested subjects by changing the stimulus mode apart occasional, slight variations of its intensity. Furthermore, a fixed cathode is mandatory to define in the individual subject the stimulus intensity proper to avoid direct myogenic artifacts.

The recorded t-SEPs showed the classic W shape common to all somatosensory evoked potentials (Desmedt, 1988; Jones, 1993).

The main t-SEP sequence (P8-N13-P19-N27-P38) is highly reminiscent, taking account for the differences in peripheral conduction time, of that of median SEP (P14-N20-P27-N35-P45) reported by Desmedt and Brunko (1980), with almost identical inter-peak latencies. However, it must be emphasized that the analogy between t-SEP P8 and median SEP P14, although highly suggestive, currently appears purely speculative since median SEP P14 is usually obtained with a non-cephalic reference, whereas trigeminal SEP P8 was recorded with a cephalic montage. The other similarity and, perhaps, the best proof of the true cortical origin of the waveform, is the progressive increase of inter-subject variability with increasing latency of the subsequent components. The same is true, except for the early positivity P8, for inter-side variability of individual peaks, probably an important diagnostic indicator, considering the prevailing unilateral involvement of trigeminal nerve in clinical practice.

Similar results were obtained by Hashimoto (1988) using air-puff stimulation of upper lip, and by Rossini et al. (2016) after electrical stimulation of the IAN territory with the main difference in both reports of the non-recognition of the early P1 positivity and poor definition of the rising phase of N1 (N13). Moreover, unlike Hashimoto (1988) and probably somehow related to the crucial difference between the two stimulation techniques, ipsilateral responses were observed in no more than 20% of t-SEPs and always of much smaller amplitude than the contralateral ones.

Trigeminal-SEPs share the well-known limitation of dermatal SEP, that is a less favorable signal-to-noise ratio, mainly due to the feebler sensory afferent volley and this is particularly true for t-SEPs where the margin of freedom in selecting the stimulus intensity is restricted by the risk of eliciting myogenic artifacts. This is supported by the mean amplitudes of t-SEP components, significantly lower, about a third, than that reported by Hashimoto (1988) after air-puff stimulation but alike that reported by Rossini et al. (2016) after electrical stimulation. That is why a significantly higher number of trials had to be averaged to obtain an adequate t-SEP definition as compared to conventional SEPs to peripheral nerve stimulation. To this respect, albeit on a purely empirical basis, the use of the Grand Average of several independent averaged blocks, separated by adequate rest periods, instead of a continuous, long-lasting recording, proved to be useful to contrast the suboptimal signal-to-noise ratio.

Dermatal SEP offers a significant clinical flexibility, allowing a selective evaluation of even restricted trigeminal skin areas.

The described, non-invasive approach does not allow recording of early far-field subcortical components, and, to this respect, it is complementary to that invasive, described by Leandri et al. (1985, 1989) that provides early t-SEP components but no consistent cortical responses. The main advantage of the described technique is that a cortical t-SEP, representing the terminal station of sensory afferents, is likely to detect any lesion at any level along the trigeminal pathway. As in many other clinical conditions, neuroimaging is ultimately entrusted with the task of defining the lesion site and often even its nature, always precluded to neurophysiology.

The Author has no competing interests to declare.

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