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PII: S1388-2457(21)00495-8
DOI: https://doi.org/10.1016/j.clinph.2021.02.396
Reference: CLINPH 2009574

To appear in: *Clinical Neurophysiology*

Received Date: 22 September 2020
Revised Date: 15 January 2021
Accepted Date: 23 February 2021

Please cite this article as: Sarnthein, J., Tomilov, M., Baag, M., Regli, L., Improving intraoperative evoked potentials at short latency by a novel neuro-stimulation technology with delayed return discharge, *Clinical Neurophysiology* (2021), doi: https://doi.org/10.1016/j.clinph.2021.02.396

Improving intraoperative evoked potentials at short latency by a novel neuro-stimulation technology with delayed return discharge

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Keywords: neurosurgery; intraoperative neuromonitoring; cranial nerve; facial nerve.

Highlights

1) The delayed discharge stimulation technology generated pulse artifacts with a tail <10 ms.
2) The signal-to-noise ratio of the evoked response was improved.
3) The method may increase the number of patients for whom intraoperative monitoring may aid in cranial neurosurgery.

Abstract

Objective: The intraoperative monitoring of cranial nerve function records evoked responses at latencies of a few milliseconds. Unfortunately, these responses may be masked by the electrical artifact of the stimulation pulse. In electrical stimulation, the return discharge of the stimulation pulse significantly contributes to the width of the electrical artifact.

Methods: We have generated stimulation pulses with an ISIS Neurostimulator (inomed Medizintechnik GmbH) providing a novel stimulation artifact reduction technique. It delays the return discharge of the stimulating pulse beyond the latency of the expected physiological response. This delayed return discharge is controlled such that no unintended physiological response is evoked.

Results: In 21 neurosurgical interventions with motor evoked potentials of the facial nerve (FNMEP), the stimulation method generated a stimulation pulse artifact with reduced tail duration. Compared to conventional stimulation with immediate return discharge, the signal-to-noise ratio of the physiological response may improve with the novel stimulation method. In some surgeries, only the novel stimulation method generated clearly identifiable response signals.

Conclusions: The reduced width of the stimulation artifact extends the toolbox of intraoperative monitoring modalities by rendering the interpretation of cranial nerve evoked potentials more reliable.

Significance: The novel technique enhances the number of patients for whom intraoperative monitoring may aid in cranial neurosurgery.

1 Introduction

Microneurosurgery of the skull base carries a significant risk of impairing cranial nerve function (Yaşargil, 1984). Among the technical measures to preserve cranial nerve function, intraoperative neurophysiological monitoring (IONM) has become mandatory (Acioly et al. , 2013, Deletis et al. , 2016). During surgery, IONM serves to communicate impending nerve damage to the surgeon and to predict the postoperative neurological state.

For continuous monitoring of cranial nerve motor function, transcranial electrical stimulation (TES) allows activation of the motor cortex and the motor pathway proximal to the surgical field and, ultimately, the recording of the motor evoked potential (MEP) in cranial nerve target muscles, for example the facial nerve MEP (FNMEP) (Akagami et al. , 2005, Sarnthein et al. , 2013, Bozinov et al. , 2015, Seidel et al. , 2020).

Despite these advantages, cranial nerve MEP monitoring has not become a standard tool of IONM yet. One reason is the close proximity between stimulation and recording sites that results in a large stimulation artifact and a short latency of the response. With standard stimulation techniques, the TES stimulation artifact may well extend over several ms after the stimulation pulse. The superposition of the artifact on the physiological response may render the interpretation of the results uncertain and thereby compromise IONM of cranial nerves.

As a novel approach, we present here a novel stimulation technique that drastically reduces the width of the simulation artifact. Among MEP of cranial nerves, the facial nerve is of highest interest – with examples of FNMEP we show that this technical advance is indeed relevant for intraoperative monitoring in cranial neurosurgery.

2 Methods

2.1 Patients

We included 21 patients (12 male, age 49 ± 21 y) who underwent neurosurgery at our institution (15 tumor and 6 vascular indications). Facial nerve function was at risk and FNMEP monitoring was performed. The collection of personal patient data and their analysis were approved and performed in accordance with the guidelines and regulations of the local research ethics committee (Kantonale Ethikkommission PB-2017-00094).

2.2 Anesthesia management

According to our standard protocol for neurosurgical interventions, anesthesia was induced with intravenous application of Propofol (1.5–2 mg/kg) and Fentanyl (2–3 µg/kg). Intratracheal intubation was facilitated by Atracurium (0.5 mg/kg), which was stopped afterwards to avoid muscle relaxation. Anesthesia was maintained with Propofol (5–10 mg/kg/h) and Remifentanil (0.1–2 µg/kg/min).

2.3 Facial nerve motor evoked potentials (FNMEP)

Intraoperative neurophysiological monitoring of the facial nerve was performed using the ISIS system (inomed Medizintechnik GmbH). Transcranial electrical stimulation was delivered by corkscrew electrodes placed at electrode sites C3 / C4 versus Cz (**Figure 1**). We chose Cz as stimulation reference to ascertain the selective hemisphere stimulation. A bite block was placed in the mouth to prevent bite injuries of the tongue resulting from activation of jaw muscles. Transcranial electrical stimulation was performed by applying anodal rectangular pulses with a constant current stimulator. We recorded the responses from facial nerve target muscles orbicularis oculi, nasalis, orbicularis oris, or mentalis with 20 mm straight needle electrodes. The ground electrode (GND) was placed half-way between the stimulation and the recording sites. Responses were amplified and filtered (250–2000 Hz) before display (**Figure 2a**).

2.4 Stimulation with the controlled delayed return discharge

In the following, we explain the difference between the standard stimulation method and the novel stimulation method with the controlled delayed return discharge. In electrical stimulation circuits, especially in the unipolar stimulation mode, there is a risk of electrolysis. In medical stimulation devices, this electrolysis is prevented by charge balancing through DC polarity compensation after stimulation. In standard devices, the charge balancing is performed by a coupling capacitor where the capacitor is discharged immediately after the stimulation pulse (**Figure 2b**). This return discharge significantly contributes to the electrical stimulation artifact in the recorded signal, superimposes the physiological response and thereby renders it difficult to interpret the recorded signal (**Figure 2a**). Our novel stimulation technique prevents this superposition. Instead of an immediate return discharge, we delay the return discharge of the stimulating pulse beyond the latency of the expected physiological response (**Figure 2c**). This is achieved by a temporal cut-off of the current flow immediately after the stimulation. As a side effect, the frequency of the hardware filters for the recording channels needs to be lowered to 0.5 Hz. The delayed return discharge is controlled such that no unintended physiological response is evoked. This technique considerably reduces the influence of the stimulation artifact on the physiological signal of interest.

The novel stimulation method is covered by a patent (Baag et al. , 2019). The safety of the device is assured by the CE (Conformité Européenne).

3 Results

3.1 Facial nerve motor evoked potential (FNMEP)

To illustrate how the novel stimulation method improves FNMEP recording, we first show one example trace of a response in facial nerve target muscles from a FNMEP elicited by the standard stimulation technique (**Figure 2a)**. A train of 3 pulses (pulse intensity 80 mA, pulse width 0.5 ms) evoked a response in the facial muscles. The current flow of the standard stimulation technique is depicted schematically in **Figure 2b.** A single control pulse delivered 40 ms before did not evoke a response (data not shown for clarity). The responses in **Figure 2a** show a variety of latencies and are polyphasic to a varying degree. Common to all responses is the large transient of the stimulation artifact that is superimposed on the physiological response. While the response in the orbicularis oris and mentalis muscles can be clearly discerned, the response in the orbicularis oculi muscle is difficult to identify. The current flow of the novel stimulation technique is depicted schematically in **Figure 2c**: the return discharge current flows only after a delay of 50 ms and with a flattened time course. Therefore the transient of the stimulation artefact as can be seen in **Figure 2d**: the FNMEP muscle responses are clearly more distinguishable from the stimulation artifact and easier to interpret. The improvement is most striking here for the orbicularis oculi muscle.

To give an overview over the usefulness of the novel stimulation method with delayed discharge, we have collected data during surgery in 21 patients (**Figure 3)**. For better comparison, we show the FNMEP response of the orbicularis oris muscle only. Compared to the standard stimulation technique (grey lines) with the wider stimulation artefact, the novel stimulation technique with the narrower stimulation artefact (black lines) renders the interpretation of the curves more reliable.

4 Discussion

4.1 Recordings

Given the large amplitude of the stimulation artifact and the small amplitude of the signal, FNMEP responses could not always be identified unambiguously with conventional stimulation. An important cause for this ambiguity was the width of the stimulation artifact with the standard stimulation technique. This was especially striking in surgeries where the stimulation intensity had to be increased and the stimulus artifact presented with a larger amplitude. When delaying the return discharge with the novel technique, the situation signal-to-noise ratio improved in some surgeries as illustrated in **Figures 2, 3.**

The novel stimulation technique improved the width of the stimulation artefact also in the muscle potentials that were evoked in other cranial nerve target muscles. Since facial nerve monitoring is most often required in the surgeries affecting cranial nerves in our institution, we focused here on the FNMEP.

4.2 Other methods to improve signal-to-noise ratio in FNMEP

The most obvious method to reduce the stimulation artefact in FNMEP is to reduce the stimulation intensity. However, the required stimulation intensity depends on several factors, among them the choice of sites for stimulation electrodes. Please note that the novel stimulation method with delayed return discharge has no effect on the required stimulation intensity.

The transient of the stimulation artefact has a slow decay compared to the muscle response (**Figure 2, 3**). The frequency for the high-pass filter must therefore be chosen adequately, usually at 250 Hz. However, the filter may also diminish the muscle response. The delayed discharge reduces the width of the stimulation artefact at its origin without further constraining filters, which constitutes a conceptual advantage.

Another method to mitigate the effect of the wide stimulation artefact would be to alternate between anodal and cathodal stimulation pulses, which is a standard technique in electrophysiology. When averaging over several alternating stimulations to obtain the evoked potential, the stimulation artifact will be minimized in the average. However, to elicit FNMEP, anodal stimulation is required because when stimulating motor cortex, anodal stimulation elicits FNMEP responses at much lower thresholds than cathodal stimulation. Therefore, we always apply anodal stimulation and, consequently, charge balancing always requires cathodal current. Since alternating stimulation is not possible for FNMEP, the delayed return discharge is of particular advantage.

4.3 Limitations and strengths

We have presented here a novel technique in the light of 21 examples, which is not a clinical study. For **Figures 2** and **3**, we have selected examples to illustrate the advantages of the delayed return discharge. In daily practice, intraoperative recordings may vary considerably depending on several factors. Clearly, even without delayed return discharge it is possible to obtain meaningful FNMEP (Akagami et al. , 2005, Acioly et al. , 2013, Sarnthein et al. , 2013, Bozinov et al. , 2015, Deletis et al. , 2016, Seidel et al. , 2020). Conversely, in spite of the delayed return discharge, meaningful results may not be achieved in some surgeries. Furthermore, as a limitation of the novel technique, lowering the frequency of the hardware filters for the recording channels to 0.5 Hz may change the shape of the motor evoked potentials also in other recording windows. In our current practice, we weigh the advantages and disadvantages of the novel method in each surgery. Still, in our experience, we achieved meaningful results more often with the delayed return discharge.

5 Conclusions

The technique presented here improves the signal-to-noise ratio of evoked potentials with short latency. The reduced width of the stimulation artifact extends the toolbox of intraoperative monitoring by rendering the interpretation of cranial nerve evoked potentials more reliable. We have presented examples for this technical advance that opens the monitorability of short latency potentials for a larger group of patients. This increases the number of patients for whom intraoperative monitoring may aid in cranial neurosurgery.

Acknowledgements

We thank Peter Roth for providing the artwork of Figure 1. The artwork has already been published earlier (Sarnthein et al. , 2013).

Author contributions

J.S. designed the experiments and performed recordings. M.T. and M.B. invented the novel stimulator and prepared the figures. L.R. provided patient care and performed surgery. J.S. and M.T. wrote the manuscript. All of the authors reviewed the final version of the manuscript.

Competing interests

M.T. and M.B are employees of inomed Medizintechnik GmbH. J.S. is member of the inomed scientific advisory board and has received speaker fees for giving presentations at inomed in-house courses on IONM.

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Figure captions

Figure 1. Facial nerve motor evoked potential electrode placement.

For transcranial electrical stimulation (TES), the anodal electrode is placed at site C4. The recording electrodes are placed in target muscles of the facial nerve: M. orbicularis oculi, M. orbicularis oris and M. mentalis. The ground electrode (GND) is placed half-way between stimulation and recording sites. The yellow arrows indicate the current flow of the stimulation artifact that includes the return discharge. We thank Peter Roth for providing the artwork of Figure 1. The artwork has already been published earlier (Figure 6 in Sarnthein et al., 2013).

Figure 2. Facial nerve motor evoked potential.

a) Conventional stimulation of the facial nerve motor evoked potential (FNMEP). Transcranial electrical stimulation (TES) causes the artifacts of the pulse train at time lags [0, 2, 4] ms. All stimulation pulses are anodal at electrode C4 to stimulate the underlying motor cortex at the face area. The pulse train elicits polyphasic muscle responses at various latencies. The return discharge after the stimulation pulse is superimposed on the muscle responses. For small and early portions of the responses, interpretation is difficult.

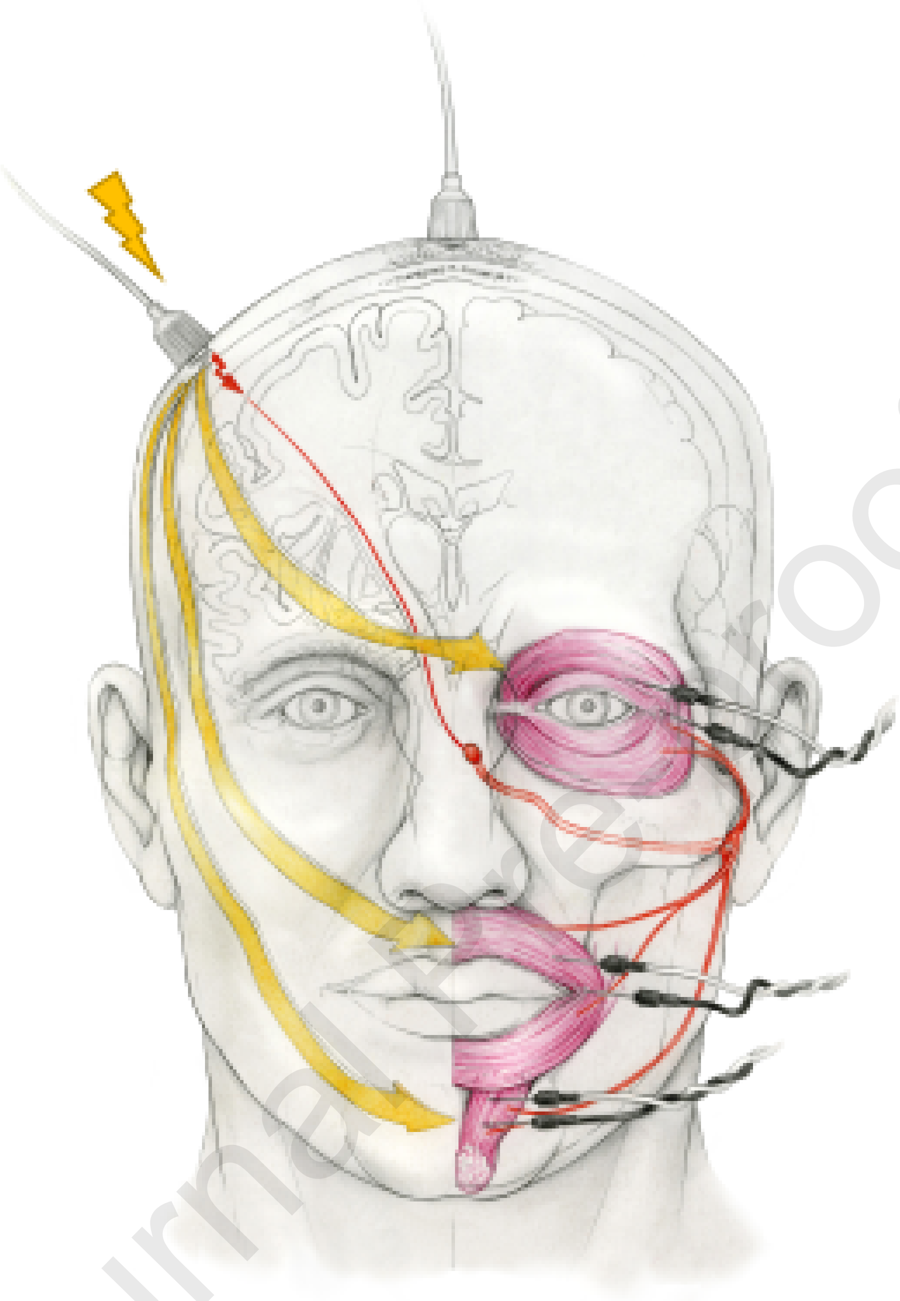
b) Current flow during conventional stimulation with a single pulse followed by a train of three pulses. Since all pulses are anodal there is a risk of electrolysis due to DC polarization. Electrolysis is prevented by DC polarity compensation immediately after stimulation. This charge balancing uses a coupling capacitor. The passive discharge of the coupling capacitor causes a current spike with opposite polarity to the stimulus and exponential decay of the charge. The resulting discharge curve depends on the intensity and duration of the stimulus and the capacitor used.

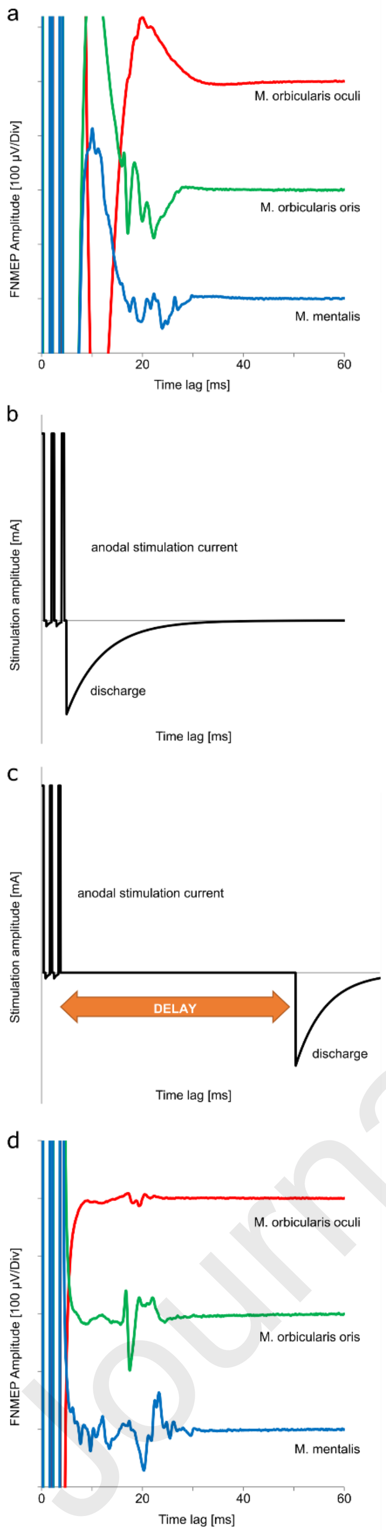
c) Current flow with delayed return discharge. The goal of the novel stimulation method is to obtain no superposition of the charge balance on the response of interest. The method exploits that the response has limited duration after stimulation. The goal is achieved by delaying the discharge curve until after the duration of the response (orange arrow). Thus, the DC polarization is prevented without the negative effect of the immediate discharge superimposed on the response of interest.

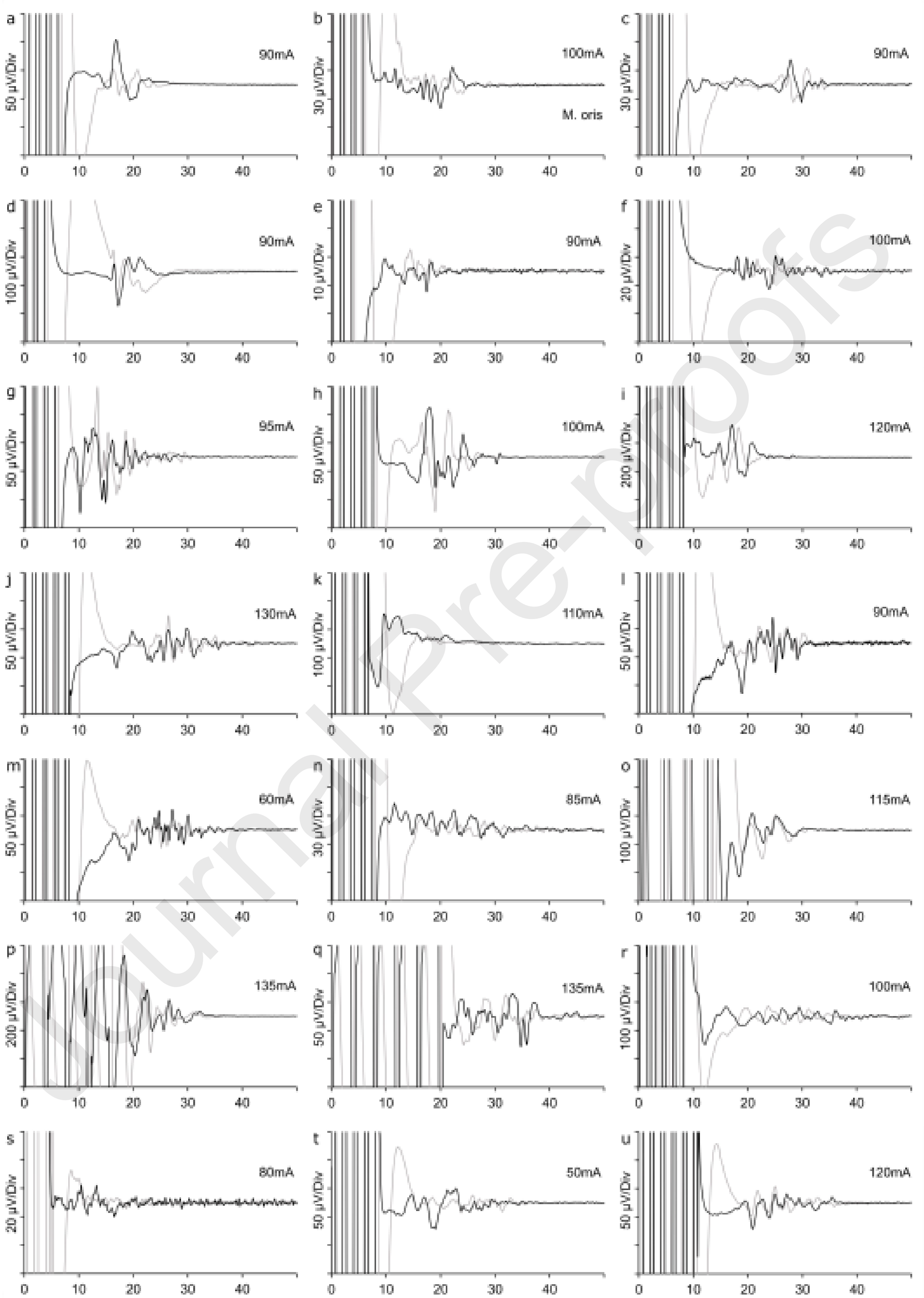
d) Stimulation of the FNMEP with delayed return discharge. The stimulation artifact extends less than 1 ms after the stimulation pulse. Therefore, the early small components of the relevant stimulus response signals are clearly visible. In particular, the response in the M. orbicularis oculi becomes amenable to interpretation.

Figure 3. Examples of FNMEP with and without delayed return discharge.

Recording of the facial nerve motor evoked potential (FNMEP) at M. orbicularis oris with delayed return discharge (black curves) and without delayed return discharge (grey curves). The recording in each panel was taken from a different surgery. The stimulation artefacts are clearly visible. The stimulation intensity is given in each panel. X-axis: Time lag [ms].




a
FNMEP Amplitude [100 µV/Div]
M. orbicularis oculi
M. orbicularis oris
M. mentalis
0
20
40
60
Time lag [ms]
b
Stimulation amplitude [mA]
anodal stimulation current
discharge
Time lag [ms]
c
Stimulation amplitude [mA]
anodal stimulation current
DELAY
discharge
Time lag [ms]
d
FNMEP Amplitude [100 µV/Div]
M. orbicularis oculi
M. orbicularis oris
M. mentalis
0
20
40
60
Time lag [ms]


a
90mA
50 µV/Div
b
100mA
M. oris
30 µV/Div
c
90mA
30 µV/Div
d
90mA
100 µV/Div
e
90mA
10 µV/Div
f
100mA
20 µV/Div
g
95mA
50 µV/Div
h
100mA
50 µV/Div
i
120mA
200 µV/Div
j
130mA
50 µV/Div
k
110mA
100 µV/Div
l
90mA
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m
60mA
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n
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q
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r
100mA
100 µV/Div
s
80mA
20 µV/Div
t
50mA
50 µV/Div
u
120mA
50 µV/Div
0
10
20
30
40