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Origin of the facial long latency responses elicited with magnetic stimulation

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Summary With magnetic stimulation (MS) it is possible to elicit bilateral long latency facial motor responses (LLRs). Due to a relatively wide magnetic field, the site of neural activation may take place in many different structures. The purpose of this study was to determine the site of origin of facial LLRs.

The motor long latency responses were recorded bilaterally on the naso-labial folds (NLFs) with reference electrodes on the nose, and on some subjects also with reference electrodes on the chin. The stimulating coil was placed in the right parietal area. LLRs obtained with MS were compared to LLRs elicited electrically at the right stylomastoid foramen, supraorbital foramen, as well as cutaneous sensory area V1 of the trigeminal nerve. In addition, right sided high intensity electrical stimuli, paired magnetic stimulation and electrical stimulation with interstimulus intervals ranging from 0 to 80 msec were also applied for comparison.

LLRs recorded with reference to the nose were always elicitable with MS as well as with the other stimulation procedures. The responses elicited with MS did not differ from those elicited electrically at various extracranial stimulation sites. With paired stimuli the second LLRs were inhibited by the preceding stimulation, whether given magnetically or electrically. In subjects with elicitable LLRs with chin references, the responses were always bilateral.

Based on the similar characteristics with extracranial electrical stimuli, bilateral distribution of the responses, and inhibition of the second response with paired stimuli, it is concluded that the neural origin of LLRs to MS is in the extracranial trigeminal or facial nerve branches.

Key words: Motor evoked; Trigemino-facial; Bilateral; Late response

Magnetic stimulation (MS) makes it possible to stimulate the cranial nerves, including the facial nerve, transcranially (Murray et al. 1987; Benecke et al. 1988; Maccabee et al. 1988; Schriefer et al. 1988; Rimpiläinen et al. 1991). There are several kinds of motor response of the facial nerve to MS. The short latency response is evoked at a location near the internal acoustic meatus (Rössler et al. 1989, 1991; Rimpiläinen et al. 1993). However, the neural origin of the additional motor responses with latencies of about 6–14 msec (Benecke et al. 1988, 1991; Rimpiläinen et al. 1992), and with latencies of about 30 msec (Maccabee et al. 1988; Ghezzi et al. 1992; Rimpiläinen et al. 1992) is not clear. It has been suggested that the long latency response (LLR) occurring at about 30 msec is caused by sensory trigeminal nerve activation or by a reflex mechanism to contraction of masticatory muscles (Maccabee et al. 1988; Rimpiläinen et al. 1992). The aim of this study was to determine the primary site of nerve activation for LLRs. To do this, LLRs elicited by MS and electrical stimulation were compared.

Material and methods

Subjects

Ten healthy volunteers, 6 females and 4 males, were studied. Their mean age was 41 years (range 27–58). None had had facial nerve or trigeminal disorders.

The subjects were examined at the Department of Otorhinolaryngology, University of Helsinki, after giving informed consent. The study was approved by the local ethics committee.

Stimulation technique, equipment, and stimulation sites

The magnetic coil generates a stimulating field that covers several anatomical structures, in which nerve activation may take place simultaneously. Due to artefacts caused by the magnetic field, it is technically difficult to make simultaneous nerve records within the

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area of cortex, cortico-bulbar tracts and trigemino-facial pathways. The muscle response with appropriate latency escaping the artefact reflects the nerve activation/excitation and has been found suitable for recording. Because the direct recording of nerve excitation in different pathways is impossible, indirect methods using other stimulation procedures were used for comparison to provide information concerning the site of excitation.

A series of 4 separate single electrical or magnetic stimuli, or paired electrical and magnetic stimuli, were given for each stimulation procedure described below. Interstimulus intervals between the 4 single or paired stimuli varied from 10 to 30 sec. In 2 cases, a series of 6 repetitive magnetic stimuli at 6 Hz were also given.

Two types of stimulator were used for electrical stimulation. A high voltage electrical stimulator specially designed for transcranial stimulation at the Ragnar Granit Institute, Tampere University of Technology, was used for electrical stimulation of the right temporal area, 12 cm lateral to vertex and towards the ear (Fig. 1). There were 3 different stimulation procedures with this device, each consisting of a series of 4 separate constant current impulses with intensities of 20–30 mA, 100 mA and 350–700 mA (stimulation procedures were named as T12-1, T12-2, and T12-3, respectively). The duration of each impulse was 40 μsec.

A commercially available 4-channel Nihon Kohden Neuropack Four device was also used for electrical

TABLE I

LLRs with reference electrodes on the nose. I = ipsilateral, C = contralateral. See text for further explanations.

Stimulation method	Number of subjects	Rec side	Latency (msec)	S.D. lat	Amplitude (mA)	S.D. amp	Duration (msec)	S.D. dur
MS	10	I	28	2.5	0.24	0.21	40	13
		C	28	2.5	0.21	0.16	40	15.7
FS	10	I	31	3.3	0.19	0.06	45	15.8
		C	31	3.1	0.17	0.09	45	15.4
NSO	10	I	31	3	0.27	0.11	54	12.2
		C	31	3.1	0.21	0.09	56	12.5
T12-1	7	I	32	4.5	0.11	0.04	45	10.6
		C	33	4.2	0.12	0.05	44	9.4
T12-2	6	I	30	2.1	0.19	0.06	52	18.3
		C	31	3.1	0.14	0.04	53	18.8
T12-3	9	I	29	1.2	0.29	0.12	52	18.2
		C	28	2.2	0.25	0.15	54	16.4
T12	7	I	35	6.9	0.11	0.04	46	8.1
		C	35	6	0.09	0.03	45	8.2
F9	6	I	35	3.7	0.14	0.07	48	9.8
		C	36	4.6	0.13	0.06	45	11
F6	6	I	33	3.4	0.19	0.07	61	16.9
		C	34	2.8	0.17	0.07	59	15.2
FS-MS-0	7	I	28	2.1	0.22	0.14	42	16
		C	27	3.5	0.26	0.19	47	18
FS-MS-2	8	I	30	2.2	0.24	0.13	40	16.6
		C	28	4.1	0.27	0.2	44	15.8
FS-MS-80	8	I	31	2	0.13	0.04	40	13.4
		C	31	3.1	0.14	0.08	40	13.1
MS-FS-2	8	I	29	1.5	0.20	0.12	37	12.3
		C	28	4.2	0.26	0.22	38	13.4
MS-FS-80	8	I	29	2	0.19	0.11	40	16.9
		C	28	3.2	0.20	0.14	40	19.9
NSO-MS-0	7	I	29	1.9	0.28	0.14	45	19.2
		C	26	3.4	0.26	0.18	46	20.5
NSO-MS-2	8	I	29	2.3	0.26	0.15	47	18
		C	28	3.1	0.28	0.22	48	19.5
NSO-MS-80	8	I	31	1.6	0.24	0.08	47	18.9
		C	30	1.9	0.19	0.12	49	19.6
MS-NSO-2	8	I	30	2.8	0.20	0.07	38	7.1
		C	28	3.4	0.22	0.15	38	7.9
MS-NSO-80	7	I	28	2.6	0.23	0.15	40	17.4
		C	27	3.8	0.27	0.24	41	20

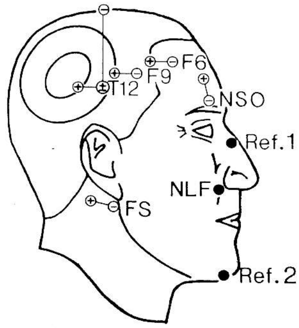


Fig. 1. When the constant current stimulator was used the cathode was positioned 12 cm lateral to the vertex (T12), 3 cm anterior to vertex and 9 cm lateral to the midline (F9), or 6 cm anterior to vertex and 6 cm lateral to the midline (F6). Cathodal stimuli at the stylomastoid foramen and at the supraorbital foramen on the sensory supraorbital nerve are described as FS and NSO, respectively. The anodes were positioned at a distance of 2.5 cm from the cathodes. When the special high voltage electrical stimulator was used the stimulating electrodes were placed at vertex (cathode) and 12 cm lateral to vertex (anode). In magnetic stimuli the center of the coil was placed 3 cm posterior to the vertex and 6 cm lateral to the midline. Recording of the responses took place bilaterally at naso-labial folds (NLF) with reference electrodes on the nose (ref. 1) or chin (ref. 2).

TABLE II

Bilateral LLRs with reference electrodes on the chin. Number of subjects with elicitable LLRs/total number of subjects examined.

Procedure	Response positive
MS	3/3
FS	2/4
NSO	4/5
T12-1	2/2
T12-2	2/2
T12-3	3/3

stimulation. The duration of the electrical impulses was 0.2 msec. The series of 4 constant current impulses of 18–30 mA and 10–18 mA were given at the stylomastoid foramen (FS) and at the supraorbital foramen of the sensory supraorbital nerve (NSO), respectively. In addition, the electrical extracranial constant current stimuli with stimulation intensity of 30 mA were given at 3 other sites on the right side: 12 cm lateral to the vertex, 3 cm anterior to vertex and 9 cm lateral to the midline, and 6 cm anterior to vertex and 6 cm lateral to the midline. Stimulation locations were identified as T12, F9 and F6, respectively (Fig. 1).

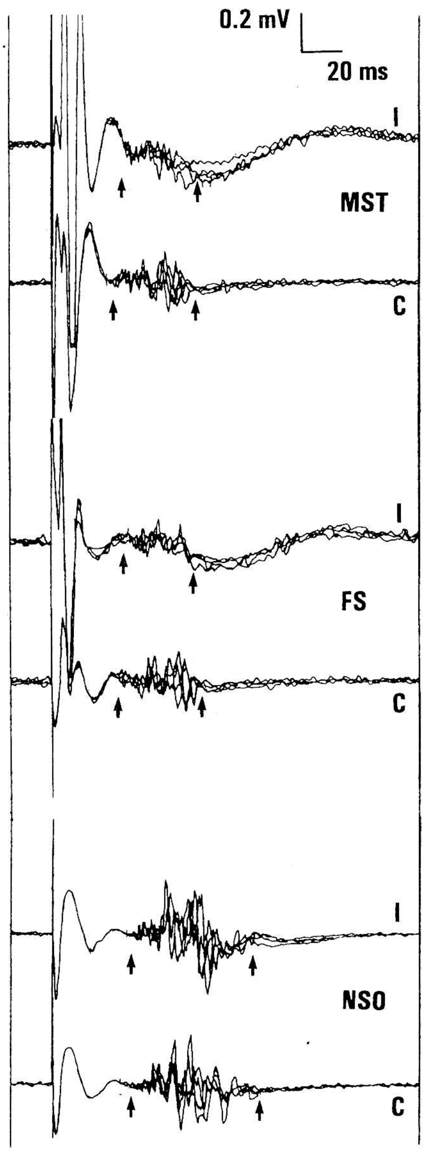
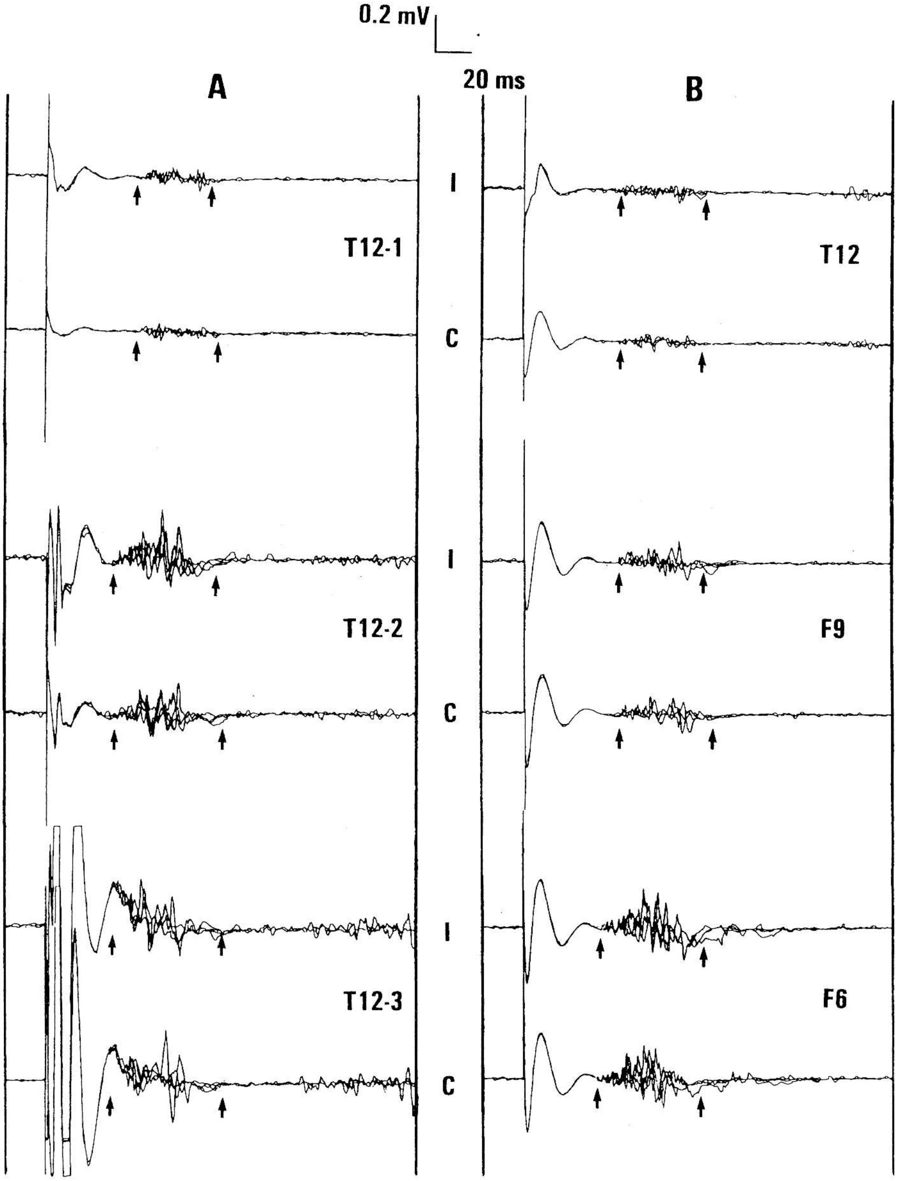


Fig. 2. LLRs with 3 stimulation techniques in 1 subject; MS = magnetic stimulation, FS = electrical stimulation at the stylomastoid foramen, NSO = electrical stimulation at the supraorbital foramen. In each stimulation procedure, 4 separate responses were recorded bilaterally from the naso-labial folds. The responses are superimposed in the figure. Black arrows indicate the beginning and end of the responses. I = ipsilateral response, C = contralateral response.


0.2 mV
20 ms
A
B
I
T12-1
C
T12
I
T12-2
C
F9
I
T12-3
C
F6

MS were delivered after positioning the coil tangentially over the right parietal area. The center of the coil was 3 cm posterior to the vertex and 6 cm lateral to the midline (Fig. 1). Eight of the subjects were studied with a Cadwell MES-10 stimulator with a round coil having an outer diameter of about 9 cm and inner diameter of about 4.1 cm. Two subjects were examined with a Dantec Magpro stimulator supplied with a round coil having an outer diameter of about 10 cm and inner diameter of about 5.8 cm. In these two cases, repetitive MS was also applied. The current output of the Cadwell MES-10 was that of a decaying sinusoid. In the Dantec Magpro the pulse was biphasic. The durations of the first major phase of the pulses were 70 μsec and 100 μsec, respectively.

The Cadwell magnetic stimulator was also synchronised to the Nihon Kohden electrical stimulator for paired stimuli with interstimulus intervals of 0, 2, 30 and 80 msec for each pair (simultaneous stimulation and repetition rates 500/sec, 33/sec, 12.5/sec, respectively). The electrical stimulation at FS and NSO preceded MS and vice versa. Each of the paired stimuli with different intervals were repeated 4 times with an interval of 10–30 sec.

MS, FS and NSO were performed in all subjects. For other stimulation procedures, the number of subjects varied from 6 to 9. The number of subjects in each stimulation procedure is shown in Table I. Additional stimulation procedures with the reference electrode on the chin were performed in 5 subjects. Table II shows the number of subjects in each stimulation procedure with chin references.

Recording procedure

The recording of the responses was performed using surface Ag/Ag-Cl electrodes placed bilaterally on the naso-labial folds (NLF) with reference electrodes ipsilaterally at the level of the nasal bone. Also NLF recording with reference electrodes ipsilaterally at the chin was used in some of the subjects (Table II).

A series of 4 responses was recorded bilaterally in each stimulation procedure. The latencies, amplitudes and durations were calculated as a mean of the 4 single responses. The latencies of LLRs were measured from the beginning of the deflection. The amplitude was the maximum peak-to-peak voltage difference. The duration was calculated from the onset to the end of the response.

Statistical analysis

A t test was used to compare the significance of the differences. A level of $P < 0.05$ was considered to be statistically significant.

Results

Reference electrode on the nose

Table I shows the responses in each stimulation procedure. The differences between the two sides of the latencies, amplitudes and durations were not statistically significant ($P > 0.05$).

Single stimuli

MS as well as electrical stimulation at FS and NSO elicited bilateral LLRs in every subject (Table I and Fig. 2). The mean latencies (ipsilateral/contralateral) were 28/28 msec (S.D. 2.5/2.5), 31/31 msec (S.D. 3.3/3.1), and 31/31 msec (S.D. 3.0/3.1), and the mean durations of the responses were 40/40 msec (S.D. 13.0/15.7), 45/45 msec (S.D. 15.8/15.4) and 54/56 msec (S.D. 12.2/12.5), respectively.

LLRs elicited with electrical extracranial stimuli lateral to, and lateral and anterior to vertex (T12, F9, F6) had on an average 3–5 msec longer latencies than LLRs elicited with electrical stimulation at NSO. There was a slight tendency for latencies to increase and amplitudes to decrease the more posterior the stimulation site (Fig. 3).

Stimulation with the prototype stimulator also elicited LLRs (Fig. 3). There was a tendency for latencies to be shorter and amplitudes to be larger with increasing stimulation intensities (procedures T12-1, T12-2 and T12-3).

Paired stimuli

LLRs were always elicitable by synchronized pairs of stimuli with MS and electrical stimuli at FS (Fig. 4), and with MS and electrical stimuli at NSO (Fig. 5), at intervals of 0, 2, 30 and 80 msec (Table I). At stimulus intervals of 0 and 2 msec it was impossible to distin-

Fig. 3. LLRs with 6 stimulation procedures in 1 subject. A: T12-1, T12-2 and T12-3 = anodal electrical stimulation 12 cm lateral to the vertex with an intensity of 30 mA, 100 mA and 700 mA, respectively. The cathode was placed on the vertex. B: cathodal electrical stimulation with a constant current of 30 mA was performed at the following 3 sites: T12 = 12 cm lateral to vertex, F9 = 3 cm anterior to the vertex and 6 cm lateral from the midline, F6 = 6 cm anterior from the vertex and 6 cm lateral to the midline. The anode was placed 2.5 cm posterior to the cathode. In each stimulation procedure, 4 separate responses were recorded bilaterally from the naso-labial folds. The responses are superimposed in the figure. Black arrows indicate the beginning and end of the responses. I = ipsilateral response, C = contralateral response.

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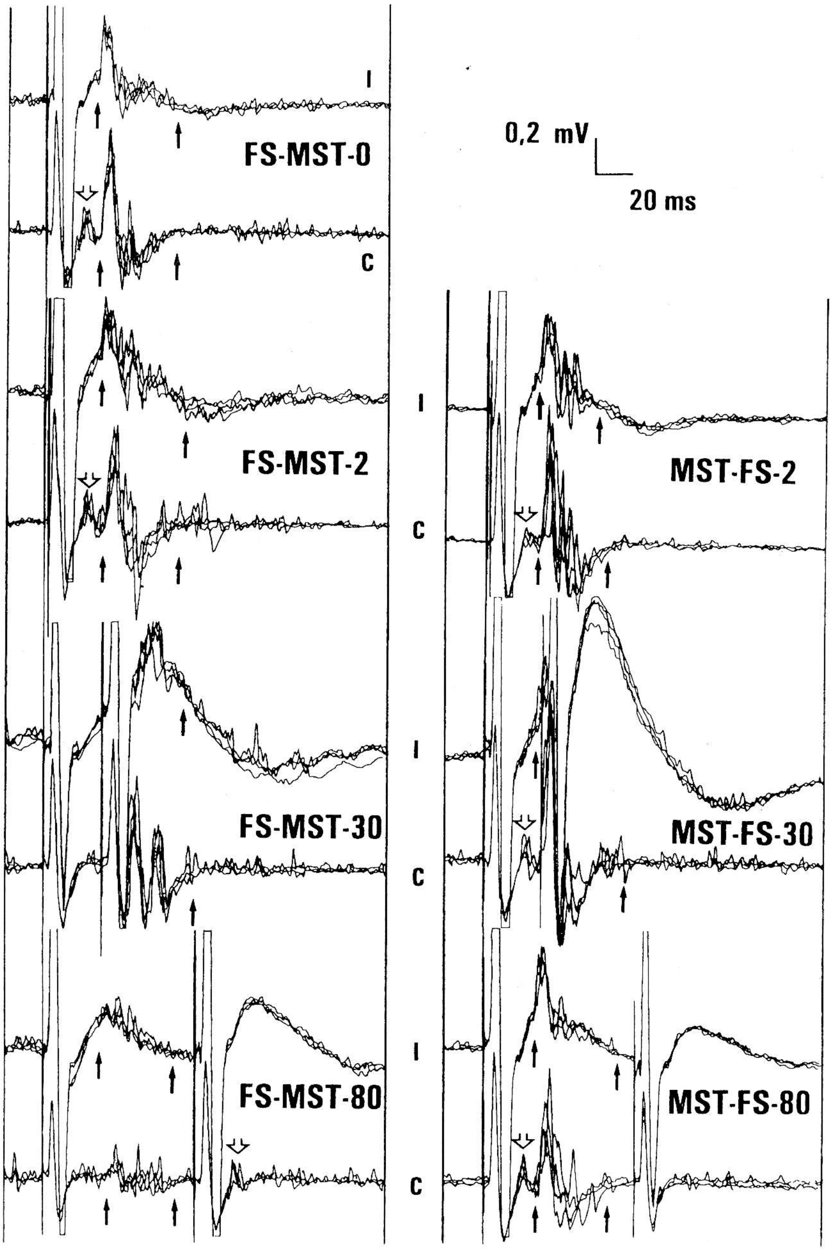
0,2 mV
20 ms
I
FS-MST-0
C
I
FS-MST-2
C
MST-FS-2
I
FS-MST-30
C
MST-FS-30
I
FS-MST-80
C
MST-FS-80

guish which one of the two impulses elicited the LLRs. At intervals of 30 and 80 msec, the latter stimulus, whether given magnetically or electrically, did not elicit another LLR. The LLRs with an interstimulus interval of 30 msec were masked by a stimulus artefact and/or a short latency response to the later stimulus, and therefore these response parameters (latency, amplitude and duration) could not be reliably calculated.

Repetitive magnetic stimuli

Repetitive MS on 2 subjects, at a frequency of 6 Hz and with a duration of 1 sec (interstimulus interval of 200 msec), elicited LLRs in response to the first stimulus. The later stimuli in the series did not elicit LLRs.

Middle latency responses (MLRs)

Although no effort was made to elicit and record the MLRs, they were clearly distinguishable contralaterally in one of the subjects (Fig. 4). MLRs followed MS with a latency of 17 msec with both single stimuli and paired stimuli. With paired stimuli the MLRs were not inhibited by the preceding electrical impulses (Fig. 4). None of the electrical stimulation procedures elicited the contralateral MLSs. Independently of MLRs there were ipsilateral responses with a latency of 10 msec with both electrical stimuli at NSO as well as with paired NSO and MS. Similar responses with about 10 msec latency were also frequently seen with NSO in other subjects.

Reference electrode on the chin

With the reference electrode placed on the chin, MS, electrical stimulation at FS and NSO elicited bilateral LLRs in 3/3, 2/4 and 4/5 subjects, respectively. Bilateral LLRs were also elicited with electrical stimuli 12 cm to the right from the vertex with different stimulation intensities (T12-1, T12-2 and T12-3) (Table II). None of the subjects had unilateral LLRs.

Discussion

In earlier reports concerning bilateral polyphasic facial LLRs, the latencies of the responses were 27–30 msec (Maccabee et al. 1988), about 30 msec (Ghezzi et al. 1992), and 28–35 msec (Rimpiläinen et al. 1992), recorded on the nasal muscle, orbicularis oculi muscle, and NLF, respectively. Based on the similarities in latencies, lateral distribution and configuration, it is most likely that the responses reflect the same nerve excitation sites. There are also responses with latencies more than 7 msec and less than 20 msec (Benecke et al. 1988, 1991; Rimpiläinen et al. 1993). They are clearly different from LLRs (Rimpiläinen et al. 1993). Unfortunately these responses are also sometimes called "long latency responses," which may cause confusion and lead to misinterpretation. Therefore it is suggested that the term LLR in association with MS should be reserved for polyphasic bilateral facial motor responses with latencies over 20 msec. Instead, a term middle latency response (MLR) is suggested here for those magnetically elicited motor facial potentials with a latency between primary ipsilateral motor response and bilateral LLRs.

With a reference electrode on the nose, bilateral, polyphasic LLRs could easily be elicited in each of the healthy volunteers by MS, as well as by each of the electrical stimulation procedures. The configurations of these responses with each of the stimulation sites and procedures much resemble each other.

When stimulating at FS, the facial nerve is located about 4 mm below the anode. The nearest points of the trigeminal auriculo-temporal nerve and cutaneous trigeminal sensory area, V3, are located about 10 mm and 15 mm away from the site of electrical stimulation at FS, respectively (Taverner 1969; Bailey 1987). When neglecting the effect of conductivity variations of different tissues, the calculated current density at the facial nerve is 3.5 times higher than in the auriculotemporal nerve and 6 times higher than at V3 (Eskola, personal communication). Because the stimulation intensity is much higher than the threshold for facial activation, each of these 3 neural areas may be activated.

The neural conduction of the bilateral orbicularis oculi muscle responses (R2 response) on stimulation of the supraorbital nerve is well established (Kimura et al. 1972; Ongerboer de Visser and Kuypers1978). The activation of LLRs at the supraorbital foramen and in the trigeminal area V1 in the scalp (procedures T12, F9 and F6) favors the idea that sensory trigeminal activation is possible in the terminal branches. The similarities in latency and amplitudes suggest that the impulses are conveyed essentially through the same pathways as in R2.

The increasing stimulation intensities at the site 12 cm lateral from the vertex (T12-1, T12-2, and T12-3,

Fig. 4. Paired stimuli with intervals of 0, 2, 30 and 80 msec. In FS-MS the electrical stimulation at the stylomastoid foramen (FS) precedes the magnetic stimulation (MS) with the given time. In MS-FS the magnetic stimulation precedes the electrical stimulation. In each stimulation procedure, 4 separate responses were recorded bilaterally from the naso-labial folds. The responses are shown superposed in the figure. Black arrows indicate the beginning and end of the responses. The open arrows indicate the contralateral middle latency responses following magnetic stimulation. I = ipsilateral response, C = contralateral response.

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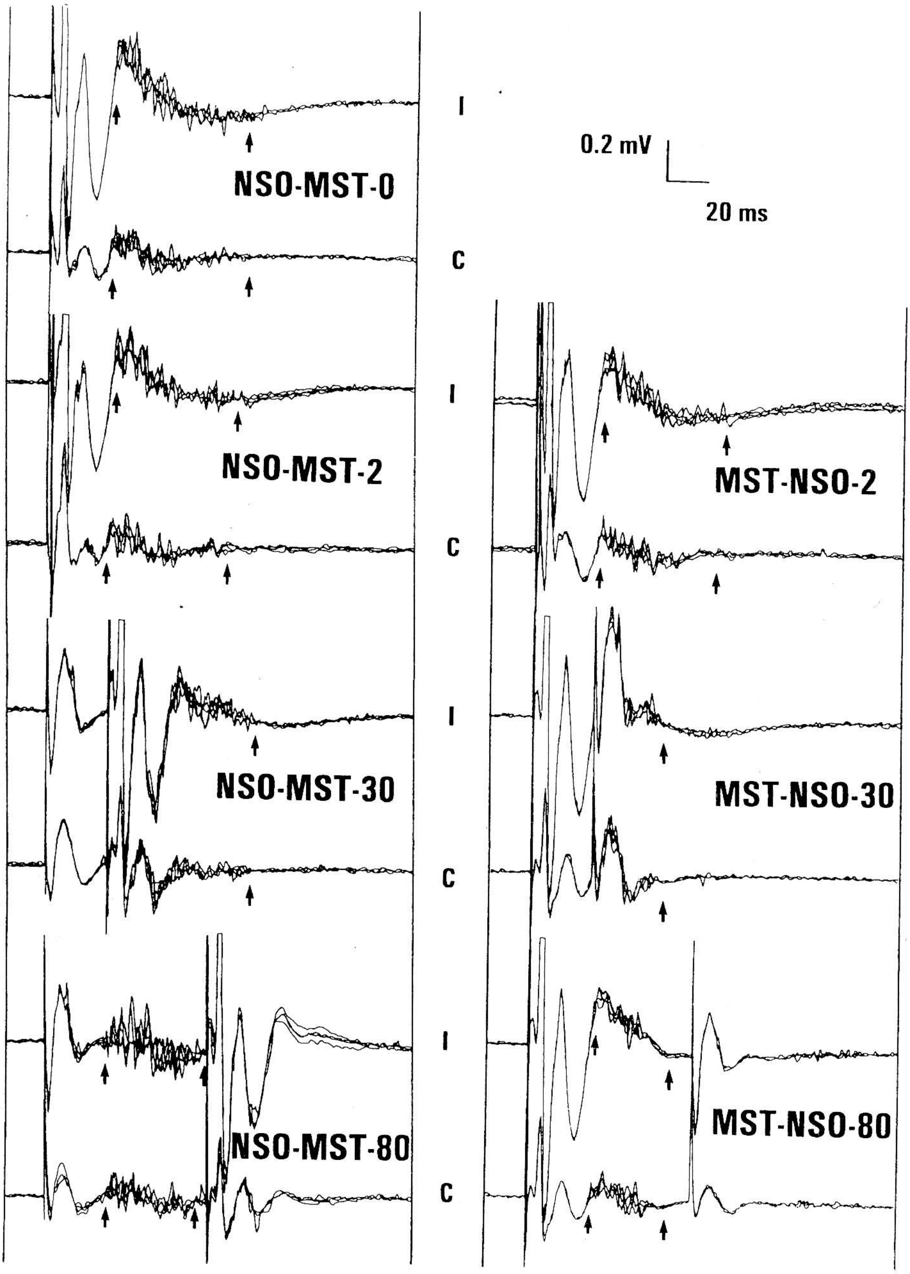

I
C
0.2 mV
20 ms
NSO-MST-0
NSO-MST-2
NSO-MST-30
NSO-MST-80
MST-NSO-2
MST-NSO-30
MST-NSO-80

respectively) caused a slight decrease in the latencies and increase of the amplitudes, possibly due to a larger stimulation area with greater intensities. Correspondingly, in electrical stimulation at NSO, F6, F9, and T12 there was a slight tendency for latencies to increase and amplitudes to decrease the more posterior the simulation site, probably reflecting excitation of more distant cutaneous trigeminal fibers.

The current density field induced by the magnetic stimulator coil is most intense just under the coil windings, but the stimulating volume increases when increasing the intensity, covering also the area where electrical stimulation of the sensory branches of the trigeminal nerve was possible (Fig. 1). The LLRs elicited by MS share the features of the responses elicited by various electrical stimulation techniques. Based on these facts, it can be suggested that the LLRs with MS are elicited within the extracranial branches of underlying trigemino-facial pathways.

With paired stimuli, the simultaneous stimulation and interstimulus interval of 2 msec did not cause any change in the responses compared to single electrical stimuli with FS, NSO, or MS alone. It is likely that the sensory fibers do not markedly facilitate the LLRs. With a short interval of 2 msec, it is impossible to distinguish whether the LLRs are elicited by the first or second stimulus. With interstimulus intervals of 30 and 80 msec, the LLRs were elicitable by the first stimulus, were it either MS or electrical FS or NSO stimulation. The second stimuli did not elicit LLRs after the first ones. In other words, the blocking of the second response takes place similarly irrespective of the stimulation order between electrical extracranial techniques and MS. This finding further supports the idea of the same mechanism of nervous activation for the respective stimulation procedures.

However, as seen in one of the subjects, contrary to LLRs, MLRs elicited with MS were not blocked with paired stimulation. In addition, another independent response with a 10 msec latency was observed following NSO (Fig. 4). It is analogous to ipsilateral R1 seen in the blink reflex. Thus, it is likely that the primary activation site of MLRs is different from that of LLRs and may possibly be located within the cortico-nuclear pathways of the facial nerve.

Bilateral LLRs were also seen with reference electrodes on the chin. The lower part of the face, including the naso-labial area, receives its cortical motor innervation purely from the opposite side (Zülch 1970). The placement of reference electrodes on the chin excludes the recording of frontal areas with bilateral cortical innervation. Thus, the finding that the bilateral LLRs are elicitable also with reference electrodes on the chin provides evidence against the assumption of cortical activation and speaks in favor of the activation of trigemino-facial pathways.

The exact site of nerve activation in MS is difficult to determine. Also the possibility that it causes activation of more than one neural structure simultaneously has to be borne in mind. Thus, with MS, the facial short latency responses are elicited transcranially in the facial nerve near the internal acoustic meatus (Rimpiläinen et al. 1993), while LLRs, on the other hand, seem to be activated extracranially, most likely through the trigemino-facial pathways.

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Fig. 5. Paired stimuli with intervals of 0, 2, 30 and 80 msec. In NSO-MS the electrical stimulation at the supraorbital foramen (NSO) precedes the magnetic stimulation (MS) with the given time. In MS-NSO the magnetic stimulation precedes the electrical stimulation. In each stimulation procedure, 4 separate responses were recorded bilaterally from the naso-labial folds. The responses are shown superposed in the figure. Black arrows indicate the beginning and the end of the responses. I = ipsilateral response, C = contralateral response.

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