Electrophysiological investigations in cranial hyperkinetic syndromes
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Chapter 1

Introduction.

In this thesis, the term cranial hyperkinetic syndromes is introduced to indicate those disorders, which are characterized by involuntary contractions of the muscles innervated by the cranial nerves. The subject of the thesis is electrodiagnostic investigations in terms of reflex studies in patients with blepharospasm, torticollis spasmodica, hemifacial spasm and patients who developed synkinesia of facial muscles following Bell's palsy (post Bell's palsy synkinesia).

Reflex studies in general and the trigemino-facial reflexes in particular, provide important information on the functional integrity of the afferent and efferent pathways, and the nuclei at the segmental level. The trigemino-facial reflexes are under control of basal ganglia and cortical structures, and these suprasegmental influences can be assessed by recording the reflexes under different physiological and pathological conditions.

Blink reflex.

Overend was the first to describe the blink reflex, which he elicited by mechanical stimulation.\(^{56}\) Examination of blink reflexes has been much improved when electrical stimulation of the supraorbital nerve and recording of subsequent compound muscle action potentials (CMAP) from the orbicularis oculi muscles was introduced by Kugelberg.\(^{86}\) He demonstrated the existence of two components of the blink reflex (see figure 1); an early ipsilateral response, R1, with a latency of about 10 to 12 ms and a duration of 5 to 10 ms and a late bilateral response, R2, with a latency of about 25 to 30 ms and a duration of 20 to 30 ms. Kugelberg's study and subsequent studies by other authors disclosed characteristics of R1 and R2 responses and their pathways in the brainstem. Ongerboer de Visser and Cruccu provided an extensive...
**Figure 1.** (A) Normal early (R1) and bilateral late (R2) responses of the blink reflex. The responses are shown from the right (r) and left (l) orbicularis oculi muscles after stimulation of the right (r*) and (l*) supraorbital nerves. (B) Diagram showing the presumed location of the bulbar interneurons subserving the two components of the blink reflex. (VII = facial nucleus; VI = abducens nucleus; Vpr = principal trigeminal nucleus; Vm = trigeminal motor nucleus; Med Tegm Field = medial tegmental field).

The common afferent limb of R1 and R2 responses is formed by A-beta fibers in the supraorbital nerve, which is part of the first division of the trigeminal nerve. The common efferent limb is the zygomatic branch of the facial nerve. R1 follows an oligosynaptic path in the pons (see figure 1). R2 is conducted along the descending trigeminal spinal tract to the trigeminal spinal nucleus in the lower brainstem, from where it follows an ipsilateral and contralateral multisynaptic pathways through the lateral reticular formation to the facial nuclei.

Rushworth stressed the difference of R1 and R2 behaviour during repeated stimulation; while R1 amplitude remains constant, R2 amplitude decreases and the response tends to disappear. R2 amplitude increases to its former amplitude when it is suggested to the patient that the next stimulation will be painful. Rushworth called this effect habituation. He also showed that loud clicks and flashes produced R2 responses. Other authors showed that R2 can also be obtained by stimulation of...
different areas of the face and by stimulation of peripheral nerves such as the median, ulnar and sural nerves as well.

After a long discussion on the origin of the electrically evoked blink reflex, more insight has been obtained by the work of Kimura, Shahani and Ongerboer de Visser. Both R1 and R2 are exteroceptive cutaneous trigeminal reflexes. However, the interaction of stimuli from other modalities or other nerves with R2 pathways remained obscure.

Sanes et al examined the effect of stimulation intensity on R1 and R2. Threshold for R1 was substantially higher than for R2. Initially, bilateral R2 responses occur with a long latency, but with increasing intensity latencies normalize. R1 threshold lowers with eyes closed and when stimulation is expected. It then may approach that of R2. R1 is a periocular response, which is present only ipsilaterally, but when the eyes are closed, or when a conditioning stimulus is given to the face or a peripheral nerve, a bilateral R1 response may be recorded in control subjects.

R1 and R2 responses differ in their behaviour during sleep. Amplitudes of both responses decrease compared to the waking state. This effect is least when REM sleep occurs. Duration of R2 responses increases substantially during REM sleep, while R1 remains relatively stable.

In children, R1 is present from birth and attains adult latency values by 24 months. R2 is absent under 20 months, varies widely between 20 and 66 months and attains normal adult values at age 6 years. Blink rates can be influenced by medication. Dopamine increases the blink rate.

Gandiglio and Fra stimulated the supraorbital nerve in 10 control subjects and recorded responses in the orbicularis oculi, orbicularis oris and mental muscles (see Table 1). Responses occurred in orbicularis oculi, less often in mental muscle and occasionally in the orbicularis oris muscle. Stimulation of the supraorbital nerve in control subjects always evokes R1 and R2 responses in orbicularis oculi, stimulation of the infraorbital nerve always evokes R2 and sometimes R1 and stimulation of the mental nerve evokes R2 in almost all subjects and rarely R1.

Each blink is caused by contraction of the orbicularis oculi and reciprocal inhibition of the levator palpebrae muscle. R1 and R2 responses of the orbicularis oculi muscle are accompanied by corresponding silent periods in the levator palpebrae muscles (so called SP1 and SP2). Eyelid movement during blink reflexes shows an early initial small ipsilateral eyelid opening at the start of R1, followed by eyelid closure about 20 ms after the beginning of R2.
Table 1. Number of responses after stimulation of supraorbital nerve in 10 control subjects.

<table>
<thead>
<tr>
<th></th>
<th>R1 ipsilateral</th>
<th>R2 ipsilateral</th>
<th>R1 contralateral</th>
<th>R2 contralateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>O Oc</td>
<td>20</td>
<td>20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>O Or</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ment</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

OOc = orbicularis oculi, OOr = orbicularis oris, ment = mental muscle.

Table 2. Methods used in blink reflex recovery studies.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Stimulation Current</th>
<th>Stimulus Duration</th>
<th>Component studied</th>
<th>Intervals</th>
<th>Rest</th>
<th>No of trials per interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kimura(82)</td>
<td>maximal R2</td>
<td>0.1 ms</td>
<td>R1:A R2:AxD</td>
<td>5-800</td>
<td>≥30 s</td>
<td>1</td>
</tr>
<tr>
<td>Berardelli et al(16)</td>
<td>3x R2 threshold</td>
<td>0.1 ms</td>
<td>R1:- R2:rect/int</td>
<td>100-3000</td>
<td>5 s</td>
<td>8</td>
</tr>
<tr>
<td>Tolosa et al(135)</td>
<td>stable R2 latency</td>
<td>0.2 ms</td>
<td>R1:A R2:AxD</td>
<td>100-1500</td>
<td>20-30 s</td>
<td>36586</td>
</tr>
<tr>
<td>Valls-Solé et al(139)</td>
<td>stable R2 response</td>
<td>?</td>
<td>R1:- R2:?</td>
<td>100-1500</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Valls-Solé and Tolosa(138)</td>
<td>welldefined R1 Stable R2 latency</td>
<td>?</td>
<td>R1:A R2:AxD</td>
<td>10-2000</td>
<td>≥30 s</td>
<td>?</td>
</tr>
<tr>
<td>Cohen et al(31)</td>
<td>maximal R2</td>
<td>0.1 ms</td>
<td>R1:rect area R2:rect area</td>
<td>150-10000</td>
<td>&gt;30-40 s</td>
<td>3</td>
</tr>
<tr>
<td>Nakashima et al(103)</td>
<td>?</td>
<td>?</td>
<td>R1:- R2:rect/int</td>
<td>100-2000</td>
<td>10-20 s</td>
<td>8</td>
</tr>
<tr>
<td>Caraceni et al(26)</td>
<td>supramaximal</td>
<td>0.1-0.5 ms</td>
<td>?</td>
<td>0-200</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

Comparison of strength and duration of stimulation, way of measurement (A = amplitude, D = duration, rect/int = rectified and integrated, rect area = rectified area), tested inter-stimulus intervals (in ms), rest between trials (in s) and number of trials averaged at each interval.
Segmental organization of the blink reflex.

The size of the compound muscle action potential evoked by direct stimulation of the facial nerve exceeds that of R.1 of the blink reflex. This means that during the blink reflex only part of the facial motoneuron pool is activated.

Several subdivisions can be made in the facial nucleus. In the cat, periocular muscles are innervated by the intermediate part of the nucleus and perioral muscles by the lateral part. This corresponds in man to dorsal and ventral subnuclei respectively. Each part of the orbicularis oculi muscle has its own division within the intermediate subnucleus of the facial nucleus.

Anatomical examination of blink reflex pathways in the cat established several brain-stem centers, which project to the intermediate facial nucleus and retractor bulbii nucleus. As both these nuclei are active during the blink reflex, the authors suggested that their anatomical connections provide information about the pathways involved in the blink reflex. These structures are the dorsal nucleus ruber and its adjacent region, the dorsolateral pontine tegmentum and principal and spinal trigeminal nuclei, the ventral part of the lateral pontine tegmentum around the level of the motor trigeminal nucleus and the medial tegmentum at the level of the hypoglossus nucleus. The latter two are premotor areas and send many fibers to the intermediate nucleus, while a connection exists between the medial medullary tegmentum and the lateral pontine tegmentum. R.1 is described as a simple oligosynaptic reflex. For R.2 the authors proposed two independent pathways; one begins in the spinal trigeminal nucleus, and leads via the superior colliculus, the parapontine reticular formation and the medullary blink premotor area to the intermediate nucleus and the lateral nucleus; the other leads via the same beginning, the red nucleus and pontine blink premotor area to the facial nucleus. There is no doubt that in man bilateral ascending fibers, involved in the generation of R.2, are located in the medial part of the lateral reticular formation in the caudal medulla oblongata, but how the rostral path before the facial nucleus is reached is not known. The multiple synapses involved in R.2 may be restricted to the reticular formation, but connections with mesencephalon or thalamus have also been proposed.

Facial nucleus.

Cortical fibers in the cat end in the reticular formation, but not directly on the facial nucleus. In man, besides this indirect connection, direct fibers to the facial nucleus have been shown. Traditionally, it has been held that the facial subnucleus, which innervates periocular muscles, receives bilateral cortical fibers, while the part which innervates perioral muscles has only a contralateral cortical connection. This is, because in central facial paresis periocular muscles are less paretic than perioral muscles. Although Kuypers in his work on corticobulbar connections in man confirms this,
his actual results show almost the same amount of bilateral cortical innervation of the ventral (perioral) and dorsal (periocular muscles) subnucleus.

Jenny and Saper\(^7\) proposed another mechanism for the different behaviour of periorcular and perioral muscles in central facial paresis in their study on Macaque monkeys. They showed that the ventral subnucleus receives much more cortical input than the dorsal subnucleus. Loss of central control will, thus, lead to less paresis of perioocular muscles.

Suprasegmental organization of the blink reflex.

Habituation as an important characteristic of the R2 response of the blink reflex was introduced by Rushworth.\(^12\) Repeated stimulations lead to a decrease of R2 amplitude, while R1 amplitude remains stable. This effect is most often attributed to a change of excitability of brainstem interneurons.\(^8\) In polysynaptic R2 pathway more interneurons are involved than in oligosynaptic R1 pathway and, thus, inhibitory activity from other centers in the brain may control R2 amplitude to a larger extent.

Boelhouwer studied R1 and R2 behaviour after repeated stimulations in control subjects. He showed that R1 conditioning and test amplitudes gradually declined during a long examination, but that repeated stimulations led to a relative increase of test stimulus amplitude, i.e., facilitation.\(^18\) Facilitation is stronger when the subject has to perform a task in response to the test stimulus. R2 amplitude rapidly declines on repeated stimulation. Although habituation is strongest at short interstimulus intervals, it can be shown even after intervals as long as 30 seconds.\(^18\) R2 facilitation only occurs when the test stimulus is presented before the conditioning stimulus, simulating a situation of anticipation.\(^20\)

Blink reflex R2 habituation is not produced exclusively by supraorbital nerve stimulation. Repetitive auditory and visual stimuli have also been shown to lower R2 amplitude. Bimodal stimulus pairs also induce an increased habituation.\(^11\) Conditioning stimuli to trigeminal, median and sural nerves result in habituation of the test R2 response after trigeminal stimulation.\(^11\) The underlying physiological mechanism of habituation is still unclear. Studies of the trigeminal spinal tract and nuclei in cats revealed a cortical inhibitory or an excitatory influence on cells in the lateral reticular formation bordering on the spinal trigeminal nuclei. These cells received input from trigeminal tactile cutaneous afferents.\(^35\) The cortical area which controls perioral sensation appeared to be larger than that controlling periocular sensation.\(^36\) Besides cortical control, there was evidence of local presynaptic inhibition in afferent fibers in the spinal tract, presumably, from brainstem interneurons.\(^34\) Although electrical cutaneous stimulation was frequently used in these studies, blink reflexes have not been specifically examined.
In habituation of the blink reflex in humans, a role of local brainstem presynaptic inhibition has been demonstrated.116,117 There are no specific studies of cortical or basal ganglia influences on habituation in man.

Cortical control of the blink reflex in human disease has been studied by several authors.37,38,84,112 Ongerboer de Visser showed that lesions of the lower third of the postcentral region led to diminished, delayed or even absent R2 responses, particularly the contralateral R2.112 Other authors suggested that cortical lesions can cause both inhibition and facilitation.37,38,84 Kuypers87 showed cortical connections with bilateral trigeminal nuclei in an anatomical study in man, and the same connections were presumed in a physiological study in cats.35

In a study using functional MRI, cortical activation patterns in the supplementary eye field and the parietal eye field were observed during voluntary blinks.21

The basal ganglia exercise an inhibitory action upon brainstem structures, and hereby regulate the sensitivity of these structures to cortical activity.28

**Blink reflex recovery curves.**

Different methods of studying habituation quantitatively have been developed.82,115 Kimura's method of calculating blink reflex recovery curves has been used in many studies.16,26,30,31,82,135,138,139 He introduced paired stimulation technique. Because of the relation between habituation and the time interval between stimuli, he studied R1 and R2 amplitudes at various interstimulus intervals between the conditioning stimulus (first stimulus) and the test stimulus (second stimulus). The test stimulus amplitude was expressed as a percentage of the conditioning stimulus amplitude at each interstimulus interval (figure 2). The resultant graph is the blink reflex recovery curve. In this way he demonstrated that in a group of patients with Parkinson's disease R2 habituation was significantly less than in a group of control subjects. R1 recovery curves showed no differences between groups. He explained the different behaviors of the R1 and R2 recovery curves with the different number of interneurons involved. He argued that a normal R1 recovery curve meant that the change in motoneuron excitability is relatively small in Parkinsonism, and that the abnormal R2 recovery curve indicates that Parkinson patients show an increased excitability of brainstem interneurons.

Other investigators used the same method of recovery curve calculation, but they used different stimulation intensities, stimulus duration, number of tests at each interval, pauses between tests and different methods of amplitude calculation (see table 2).
**Figure 1.** Recordings of R1 and R2 blink reflex recovery curves from a control subject. (A) Average of six successive trials at each interstimulus interval, filtered and rectified. (B) Recovery curve of R1 responses and (C) of R2 responses from the same subject.
Blink reflex in cranial hyperkinetic syndromes.

Reflexes in blepharospasm.

Blepharospasm is a form of focal dystonia, commonly characterized by variable episodes of involuntary closure of the eyelids.\textsuperscript{5} Blepharospasm may occur following pathological alteration of basal ganglia activity.\textsuperscript{92} However, lesions in the midbrain,\textsuperscript{71} putamen\textsuperscript{42} or even the pons\textsuperscript{7} have also been proposed as the cause of blepharospasm. In cats, low-frequency stimulation of the putamen (2-6/s) leads to closure of the eyes, while high-frequency stimulation (30/s) results in opening of the eyes.\textsuperscript{40} However, there has been much controversy about the organic or psychologic origin of symptoms in focal dystonias in the past.

In 1985 Berardelli et al\textsuperscript{16} were the first to publish abnormalities of neurophysiological examinations in 16 patients with oromandibular dystonia and blepharospasm. They found abnormalities of blink reflex responses, blink reflex recovery curves, corneal reflexes and masseter muscle inhibitory reflex. Latencies of R1 and R2 were normal, but R1 amplitudes and R2 amplitudes and duration were increased. Bilateral R1 responses were absent in controls, but they appeared in six out of 16 patients. An abnormal R2 recovery curve in the patient group indicated a decrease of habituation compared to the control group. Results of R1 recovery were not mentioned. The authors used Kimura's arguments to support their hypothesis that there is an increased excitability of brainstem interneurons and concluded that this was caused by a decreased inhibitory influence from the basal ganglia.

It was later confirmed that R1 recovery curves were normal, while R2 recovery curves showed decreased habituation in patients with cranial dystonia and spasmodic torticollis.\textsuperscript{114,135} The abnormalities of R1 amplitude and R2 amplitude and duration could not be reproduced in a later study,\textsuperscript{114} but R2 duration was increased bilaterally in another study.\textsuperscript{27}

In a study of perioral reflexes in five patients with orofacial dyskinesia, the authors used mechanical stimulation around the mouth and electrical stimulation of the infraorbital and mental nerves.\textsuperscript{136} Early and late responses were found in the perioral muscles. Mechanical stimulation evoked significantly larger late responses in patients than in controls. Electrical stimulation of the infraorbital nerve resulted in marginally significant increase of late responses, while mental nerve stimulation showed no significant differences between the patients and controls.

Reflexes in torticollis spasmodica.

Torticollis spasmodica is also a type of focal dystonia and is characterized by involuntary deviation of the head due to contractions of the neck muscles.\textsuperscript{24}
R2 recovery curves were abnormal in several studies in patients with torticollis, while R1 recovery curves were normal compared to controls. This was attributed to the same mechanisms as in blepharospasm. There was no difference in latency, duration or amplitude of the R1 component of the blink reflex. The R2 component showed a normal latency. In five patients with torticollis spasmodica as a part of a generalized dystonia, ipsilateral R2 amplitudes were increased, and in 15 patients with isolated torticollis, they were within normal range.

Reflexes in hemifacial spasm.

The etiology of hemifacial spasm is still obscure. It has been postulated that it may be caused by ephaptic transmission, or by hyperexcitability of facial motoneurons within the facial nucleus. Vascular compression of the facial nerve root near the brainstem has been recognized by Gardner as a cause of hemifacial spasm. Jannetta popularized operative treatment. He claimed that removal of the compressing vessel from the nerve improves hemifacial spasm, but there are conflicting opinions. One criticism is that vascular compression can be demonstrated regularly at post mortem examination without the occurrence of hemifacial spasm during life. Vascular compression of the facial nerve is, however, not the only mechanism in hemifacial spasm; cerebellopontine angle tumors, Paget's disease, tuberculous meningitis, multiple sclerosis, trauma and many other causes have been reported.

Blink reflex studies in hemifacial spasm have led to contradictory results. Auger measured normal latencies and amplitudes of R1 and R2 responses. Facial nerve conduction was normal. Nielsen found an increased latency of R1 on the affected side. R2 latency was not significantly longer compared to controls, but when compared with the corresponding response on the unaffected side in the same patient, a significant increase was found. Amplitudes of both R1 and R2 were more than twice as high as those on the unaffected side and in controls. In a study by Esteban and Molina-Negro of 53 patients with hemifacial spasm, R1 latency was normal, R2 latency was shortened and R2 duration was increased. In a few cases, R1 and R2 responses were not separated. However, six patients showed a lengthened R2 response. Synkinesis was studied by supraorbital nerve stimulation and measurement in orbicularis oris. All patients showed an R1 response, and 20/23 showed an R2 response.

In 1984, Nielsen argued that ectopic excitation and ephaptic transmission, or cross-talk between demyelinated nerve fibers, which are damaged by vascular compression at the root entry zone, can explain the frequent spontaneous discharges in hemifacial spasm. Pathological studies have indeed shown some damage to facial nerve fibers. Mechanical and chemical irritation of the facial nerve at the root entry zone may lead to ectopic, local and extranuclear, excitation. Nielsen assumed that ephaptic transmission to normal nerve fibers may occur from a demyelinated, slowly conducting fiber to a less demyelinated, faster conducting fiber. He studied blink reflexes and found a delay of R1 and R2 on the affected side. He
also stimulated isolated branches of the facial nerve, using a method described by Hopf and Lowitzsch. In this way he demonstrated a late response in a facial branch which was not stimulated, and concluded that this must be a sign of ephaptic transmission. Another argument in favour of this assumption was that this late response disappeared 2-8 months after the operation according to Jannetta in 73% of 30 patients.

Møller used the same method of examination, which he called lateral spreading, during operations. He concluded that the late response was the result of hyperexcitability of motoneurons in the facial nucleus. In subsequent studies he was able to increase the probability of his view. This was done by the combination of intraoperative recording of lateral spreading and the study of blink reflexes. In one study he used a collision technique of supraorbital and facial nerve stimulations.

**Reflexes in post Bell's palsy synkinesia.**

Patients with Bell's palsy may develop synkinesia and usually show signs of damage to the facial nerve on the affected side, which can be examined by recording of the blink reflexes. Kimura et al found increased latencies and decreased amplitudes of R1 and R2 on the affected side, and Valls-Solé et al an increased R1 latency and an increased R2 amplitude. Both studies demonstrated responses in the orbicularis oculi and orbicularis oris muscles after stimulation of the supraorbital nerve on the affected side, while after stimulation of the supraorbital nerve on the unaffected side only a response in the orbicularis oculi muscle was found.

Traditionally, this response in orbicularis oris has been interpreted as a sign of faulty nerve regeneration after Bell's palsy. This interpretation has been accepted by many investigators, although hyperexcitability of facial motoneurons or ephaptic transmission has also been proposed.

A study in a monkey with synkinesia after facial nerve damage provided experimental evidence for the theory of faulty nerve regeneration. In another study in rats, the facial nerve was damaged and later horseradish peroxidase was injected in one facial nerve branch. On the unaffected side horseradish peroxidase was demonstrated in discrete subnuclei in the facial nerve nucleus, but on the damaged side it was spread throughout the nucleus.

The exact relationship of synkinesia after Bell's palsy and hemifacial spasm is not clear. Patients with Bell's palsy may develop signs which are indistinguishable from those of hemifacial spasm. Some authors seem not to make a distinction between both conditions, and in at least one study of hemifacial spasm some patients had Bell's palsy in the past.
Aim and outlines.

Electrodiagnostical studies have played an important role in providing evidence for the organic nature of focal dystonias and in investigating the underlying pathophysiological mechanisms of other cranial hyperkinetic syndromes. In this thesis, various electrodiagnostical studies were performed in patients suffering from a form of cranial hyperkinetic syndrome, namely blepharospasm, torticollis spasmodica, hemifacial spasm and synkinesia after Bell’s palsy (post Bell’s palsy synkinesia). The subjects of the studies were to improve the reflex recording and calculation techniques, to obtain data on the state of excitability of segmental and suprasegmental structures in individual patients and to obtain a better insight into underlying pathophysiological mechanisms of these diseases.

Chapter 1 gives a review of important previous neurophysiological studies in these four hyperkinetic syndromes.

Chapter 2 presents the results of recovery curve recording using two different stimulation intensities and two different computerized response measurements in order to establish the best way to separate controls and patients.

In Chapter 3, we analyzed the recovery curve indices in subgroups of patients with blepharospasm and examined possible correlations between subgroups and hyperexcitability of segmental structures.

In Chapter 4 the reflex responses in the orbicularis oculi and oris muscles during spasm-free intervals were analyzed in patients with focal dystonia.

Chapter 5 presents reflex responses, including the lateral spreading, as recorded in patients with hemifacial spasm and in patients with synkinesia after Bell’s palsy, in order to distinguish these two disorders.

In Chapter 6, the main findings of this thesis are reviewed and discussed, and some recommendations for future research are given.