Instrumental investigations in primary headache. An updated review and new perspectives

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Summary

While some instrumental techniques are clearly useful for differentiating symptomatic forms from primary headache, the usefulness of certain other techniques, neurophysiological investigations in particular, in clinical practice is still debated.

A Task Force of the European Federation of Neurological Societies has recently proposed guidelines and recommendations on the use of neurophysiological tests and neuroimaging procedures in non-acute headache. This article reviews many of the most important literature references relevant to this topic and looks at the prospects for future research.

Key words: headache, neuroimaging, neurophysiology.

Introduction

Instrumental investigations are extensively carried out in headache, primary headache in particular. While some techniques (e.g., neuroimaging) are clearly useful for differentiating symptomatic forms from primary headache, the usefulness of certain other techniques, neurophysiological investigations in particular, in clinical practice is still debated. A Task Force of the European Federation of Neurological Societies was asked to propose guidelines and recommendations on the use of neurophysiological tests and neuroimaging procedures in non-acute headache and the final version of these is in press elsewhere (1). While most of the techniques seem to be poor tools in the diagnosis of primary headaches, they have made, and continue to make, a fundamental contribution to our understanding of the pathogenesis of primary headache (1,2).

This article reviews many of the most important literature references relevant to this topic, which are broken down into two main areas: neurophysiological investigations and neuroimaging.

Neurophysiological investigations in headache

Electroencephalography (EEG)

EEG in migraine

A few controlled and blinded studies have shown slight interictal EEG abnormalities in migraine patients (3,4), with similar prevalences generally being reported in migraine with and without aura. The prevalence of definitely abnormal EEG activity is low and generally not different from that found in healthy subjects. Focal slow activity has been reported in 0-15% and spike activity in 0.2-9% of migraineurs (5,6). During visual aura, slow waves, depression of background activity amplitude, and normal EEG have each been reported (7,8). Definitely abnormal EEG with unilateral or bilateral delta activity is often recorded during attacks of hemiplegic migraine (9), and during attacks of basilar migraine with disturbed consciousness (10,11).
EEG in other headaches

EEG in tension-type headache is generally considered to be normal. Older blinded studies reported slightly lower rates of EEG “abnormality” in tension-type headache versus migraine, but healthy subjects were not studied (5,12). While normal quantitative EEG (QEEG) was found in children with tension-type headache (13), photic driving may be increased in this condition (14). Epileptiform activity has been described in cluster headache (15), but the association has not been confirmed in other studies.

Epilepsy and migraine

Some observational studies (16,17) have suggested a possible link between partial childhood epilepsy and migraine (18), a suggestion not supported, however, by one well-designed population-based epidemiological study (19). Symptoms of migraine and epilepsy coexist in some mitochondrial encephalopathies (20). Migraine-like headache may be an ictal or postictal epileptic manifestation (21,22), and conversely epileptic seizures may rarely be triggered by migraine attacks (23). Migraine-like symptoms (visual disturbances, headache and vomiting) occur in many patients with childhood epilepsy with occipital paroxysms (CEOP) (24). Patients with CEOP have occasionally been misdiagnosed with basilar migraine (25) and basilar migraine may possibly coexist with CEOP in some subjects (26). Kramer et al. (27) reported that epileptiform activity was most often found in a subgroup of children with “very brief headache”. Unequivocal epileptiform abnormalities usually suggest a diagnosis of epilepsy, and in children with occipital spike-wave activity (with or without blocking on eye opening) the probable diagnosis is CEOP.

Photic EEG driving (“H-response”) in migraine and other headaches

Gronseth and Greenberg (28) claimed that a prominent photic driving response to high flash rates is “the only abnormality consistently reported in headache patients, as opposed to controls, in studies of relatively non-flawed design”. However, the H-response is not specific for migraine and it has been found to occur frequently in post concussion syndrome and in healthy subjects when EEGs were evaluated blindly (3,29).

In a critical review of the literature, van Dijk et al. (30) reported highly variable estimates of sensitivity (ranging from 25 to 100%) and specificity (ranging from 14 to 100%). These authors correctly identified several problems associated with photic driving studies, including choice of variables, complexity of analysis methods, lack of luminosity control, and lack of information regarding time-relationships, i.e., the time preceding (and following) headache attacks (30). Genco et al. (31) reported increased driving power in adults and children with migraine with and without aura, but no abnormal rates were reported for photic driving. The driving response tended to be greater in migraine with aura compared to migraine without aura (32).

A blinded study comparing a large sample of migraine without aura patients with tension-type headache patients and controls has recently been published (14).

Photic driving power (15-30 Hz range) was found to be higher in both migraine and tension-type headache patients compared with controls. Discriminant analysis correctly distinguished the control subjects, while significant misclassification occurred among the tension-type headache and migraine patients (14). This important study is the first to address most of the methodological problems found in previous research, whose main goal—to find a useful biological marker for migraine—has yet to be achieved.

EEG frequency analysis including topographic brain mapping (QEEG).

Early QEEG studies gave somewhat inconsistent results, although a pattern of increased alpha rhythm variability (and/or asymmetry) in the headache-free phase did seem to emerge (33-35).

Fachetti et al. (36) found increased absolute alpha power asymmetry in adult migraine with aura, but this was not confirmed by Lia et al. (37). Abnormal QEEG slowing was found in 65% of 31 migraineurs (38). Lia et al. (37) found abnormal relative spectral values in 11/28 migraine patients. Neufeld et al. (38), on the other hand, found lower occipital alpha power in migraine (with and without aura) compared with healthy controls. In children suffering from migraine with aura, increased theta-alpha ratio (13), increased theta power (31,39), and normal bandpowers (40) have been found in the interictal period. In migraine without aura attacks, a slowing of posterior mean frequency, with no obvious change in absolute power, was recently reported (41). Alpha power depression followed by bifrontal and parietooccipital increased delta power has been found in children during visual aura (40) and in adult migraineurs following ischaemic arm test (42). The suggestion that QEEG abnormality can be used to predict drug response (43) should be tested in a prospective study.

Interpretation is rendered more difficult by the use of different QEEG and statistical methods, and by a lack of general knowledge of the physiological nature of various EEG rhythm generators (44). High sensitivity is reported in some studies, but information on specificity is lacking in most. QEEG studies have generally not been specified as blinded. Although the “objective” nature of QEEG may seem to obviate the need for blinding, epoch selection bias may be an unrecognized problem.

Evoked potentials

Visual evoked potentials (VEPs)

Twenty-six papers relevant to this topic were identified. All studies were primarily aimed at migraine, while tension-type headache patients featured as control groups in a few studies. Blinding was very often not mentioned; in some studies, using fully automated quantification methods, it was judged to be irrelevant. Of the 26 studies, only 8 presented data on sensitivity and specificity. Of these 8 studies, 5 met most quality criteria. These 5 studies examine different clinical approaches. The studies by de Tommaso (14,45) were based on discriminant analysis of steady-state VEPs. Migraineurs were found to have higher amplitudes in response to...
photic stimulation with frequencies of 15 to 30 Hz (14), or 21, 24 and 27 Hz (45). A sensitivity of 73% and a specificity of 63% were obtained. One problem with this approach is that discriminant analysis optimizes the differences between groups, based on a large number of variables. The two papers used different approaches, and no recommendations for simplification of the procedure were given. Discriminant analysis does not lend itself well to general application in daily practice, which requires a less complex and more robust parameter of abnormality.

Pattern-reversal VEPs were studied by Lahat et al. (46). This study compared children with migrainous and non-migrainous headaches. A distinction based on increased amplitudes in the migraine group resulted in a sensitivity of 67% and a specificity of 83%. Unfortunately, the definition of abnormality appears to have been misprinted. The authors state that 'in borderline cases the study of VEPs may prove a useful diagnostic tool'.

Tagliati et al. (47) focused on pattern reversal VEP (PRVEP) amplitude asymmetries in migraine: in 8 patients with (apparently exclusively) unilateral hemianopic aura, the degree of asymmetry was larger than in all 15 controls. This asymmetry was calculated using multiple electrode derivations. Although of interest for pathophysiological reasons, the diagnostic applicability of this test remains unclear.

Van Dijk et al. (48) found higher alpha power during 2 Hz photic stimulation in only 2/8 migraineurs, and in none of 10 controls. It was concluded that the test was not useful for diagnosis. The study investigated claims of very high sensitivity and specificity of 'fast wave' activity in the background of the EEG. However, the technique relied on subjective evaluation of this activity, and could not be replicated (49,50). Subsequent studies using the same technique were not blinded.

Auditory evoked potentials (AEPs)

No data on diagnostic yield were found, but available mean data relating to patient and control groups do not suggest that AEPs, somatosensory evoked potentials, or motor evoked potentials are useful in this respect.

Reflex responses

Nociceptive reflexes evoked at trigeminal and spinal level were used as a tool for exploring the pain control system in headache. Contradictory findings regarding the blink reflex (BR) have been reported in migraine patients. One study described an increased R2 latency (51), which another failed to confirm (52). The latter authors, in a blinded study, found no difference in the latencies of the first (R1) and second (R2) components of the blink reflex between cervicogenic headache, chronic tension-type headache and migraine patients compared with controls, reporting only an R1 latency asymmetry in cervicogenic headache.

Studies of cluster headache are more heavily affected by methodological and design bias (i.e., heterogeneous samples of patients, episodic/chronic form, in remission/in period, not-drug free, no blind observer). In an investigation of the BR, Lozza et al. (53) demonstrated a unilateral sensitization of the trigeminal pathways.

In one study, electrophysiological evaluation of the corneal reflex (CR) in cluster headache patients revealed a significant reduction of the reflex threshold on the symptomatic side, with a parallel decrease in pain threshold during the active phase, while normal values were reported during the remission period (54).

CR on the symptomatic side in cluster headache patients showed high specificity (100%) and good sensitivity (69%) in distinguishing between cluster patients in the active versus the remission period.

Abnormally decreased CR thresholds have been recorded bilaterally in patients with hemicrania continua and in chronic paroxysmal hemicrania (55). Reduction of the second component of exteroceptive suppression (ES2) duration at the temporalis muscle has been reported in chronic tension-type headache patients (35,56), a finding not confirmed by other studies (57,58). Several methodological differences may have limited the agreement of the results. Moreover, only the last two of these studies were blinded to the observer. The repeatability of the method is rather poor per se, and the variability is further increased if we consider the large number of factors possibly influencing the examination (i.e., anxiety and anticipation of pain, level of muscular effort, hormonal influences, etc.).

The reduction of the ES2 duration has been hypothesized to reflect tension-type headache severity, since originally it was found in chronic, but not in episodic tension-type headache. Normal values are found in other primary and secondary headaches, such as migraine, cluster headache, cervicogenic and post-traumatic headache, and post-lumbar puncture headache. In contrast, the ES2 is also reported to be shortened in chronic daily headache, with or without drug abuse (56).

The sensitivity and specificity of this electrophysiological test have been estimated to be 84% and 65% respectively (59), but more recent studies have not been able to confirm its potential clinical usefulness (58,60).

Unfortunately, the ES2 does not help in distinguishing between episodic tension-type headache and migraine, which may sometimes be the real clinical problem. The ES2 cannot be recommended as a diagnostic tool because of the wide range of variability, which results in an overlap with normal values.

A close relationship has been found between the subjective sensation of pain and the RIII reflex component of the nociceptive flexion reflex (NFR) of the lower limb elicited by electrical stimulation of the sural nerve (61, 62). Exploration of this reflex has been deemed interesting in headache patients since it allows evaluation of central pain processing. In fact this spinal reflex seems to be modulated by serotonergic and opiategic fibers descending from the raphe dorsalis nucleus and periaqueductal gray in particular. Only one study has been carried out in migraine patients, reporting a decreased RIII reflex threshold proportional to the headache severity. The RIII threshold seems to be decreased only in severe forms of migraine (62).

One study reported a significantly lower RIII threshold in chronic tension-type headache patients versus the control group (63), while another study (54) found a decreased ratio between subjective pain perception threshold and RIII threshold. Further investigations are needed in order to establish whether the RIII reflex could be a useful marker in headache patients.
Testing autonomic nervous system (ANS) functions

General aspects

Clinical observations, primarily, constitute the rationale for studying autonomic nervous system (ANS) functions in headache (64). ANS function changes are obvious in cluster headache and, over the past 20 years, have been extensively investigated in reference to this pain. ANS function changes are suspected to be important in migraine, too, but are less obvious in this headache form.

Migraine

Based on a literature review and an extensive investigation of patients with migraine, Thomsen et al. conclude that "clear dysfunction of the sympathetic nervous system remains to be shown ... Mild parasympathetic hypofunction with denervation supersensitivity may be present in migraine" (65,66). Results are variable however. Boiardi et al. (67), for instance, reported that the diastolic blood pressure response to sustained handgrip was impaired in 61% of migraine patients. In a recent study, no heart rate variability differences between migraine patients and control subjects were found (68). Micielli et al. (69) found increased basal pupillary diameter as well as increased light reflex contraction and dilatation velocities in migraineurs. Sensitivity was not reported but can be deduced from their data. Increased pupillary dilatation in response to phenylephrine eyedrops has also been found in migraine (70,71).

Cluster headache

A "Horner-like" pupillary dysfunction has been found in cluster headache. Fanciullacci et al. (72) found decreased responses to indirectly and directly acting sympathomimetic eyedrops. The authors found ipsilateral miosis and decreased mydriatic responses to phenylephrine, which they interpreted as denervation supersensitivity. Data regarding reliability, sensitivity and specificity are incompletely reported. Increased pupillary dilatation to phenylephrine has, however, also been reported in migraine (70,71). These tests should be investigated further and refined with the aim of developing a test protocol that might be helpful in the clinical setting.

Sweating has also been studied, by evaporimetry, in cluster headache and in short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) (73,74). The most interesting finding is ipsilateral reduced response to heating and increased response (denervation supersensitivity?) to parenteral pilocarpine, similar to first neuron (central) symptoms in Horner patients. Data regarding reliability, sensitivity and specificity are incompletely reported. The variation between subjects seems to be large. Thus it is uncertain whether the test can be developed into a useful clinical tool. More research is needed.

Heart rate variability may be slightly reduced in cluster headache (67), however, it is unclear whether results addressing disturbances of the autonomic regulation of the heart might provide information on autonomic abnormalities in cluster headache.

Evaluation of pericranial muscle tenderness (with special reference to tension-type headache)

Pericranial tenderness investigated by manual palpation

Increased tenderness upon manual palpation is one of the most consistent findings in tension-type headache patients (60-75-83). Tenderness increases with increasing frequency and intensity of the headache and is not related to the frequency of a possible coexisting migraine (79,84). Only patients with chronic tension-type headache have decreased pressure pain thresholds (PPTs) and the diagnostic sensitivity and specificity of PPTs recorded from a standardized location have been found to be very limited (77,81,85-87). The PPT seems to vary with pain intensity (88). The diagnostic information obtained by recording PPTs from tender points in headache patients has not yet been studied in detail but the method is difficult to apply in the clinical setting, as the location of tender points is highly variable both within and between patients. The PPT cannot therefore be recommended as a diagnostic test.

Electromyography (EMG)

Some studies, but not others, have reported slightly increased EMG levels in patients with chronic tension-type headache (76,80,89,90). Increased EMG activity has been found in the trapezius muscle during a pain-provoking reaction-time task (91). However, the sensitivity and specificity of EMG are very limited (81) and EMG cannot be recommended as a routine diagnostic test.

Combinations of diagnostic tests

In a general population, 87% of subjects with chronic, and 66% of subjects with tension-type headache were found to have an associated pericranial muscle disorder (81). In a clinical study, the headache of 61% of patients with the episodic and of 66% of those with the chronic subform was found to be associated with a muscular disorder (76), a result not dissimilar to the 72% recorded in a previous study, in which only EMG and pressure algometry were assessed (86). However, the specificity appeared to be very low (76,81) and the high frequency of association with muscular disorders is mainly due to the markedly increased tenderness evidenced by manual palpation. In addition, tenderness and PPTs may vary with pain intensity whereas EMG levels are largely unaffected by ongoing pain (76,81,88). It is therefore valuable to record the presence or absence as well as the intensity of headache during the clinical examination.

Neuroimaging and neurosonology in headache

Neuroradiology

In 1994, Frishberg (for the Quality Standards Subcommittee of the American Academy of Neurology) performed a meta-analysis of the existing literature from 1974 through July 1993 in order to define the yield of pathology when neuroimaging is performed to evaluate headache in patients with normal neurological examinations, and also in order to see what effect neuroimaging
has on patient health outcomes (92,93). To this end, 17 studies were selected for analysis. In this series of studies, a total of 1,825 CT scans and MRI investigations were performed in patients with undefined headaches (i.e., not defined in the paper) and normal neurological examinations. In this series, 21 tumors, 6 arteriovenous malformations (AVMs), 3 aneurysms, 5 subdural hematomas, and 8 cases of hydrocephalus were found. Thus, an abnormality that might account for headache as a symptom was found in 2.4% of patients (92). In the same meta-analysis, 897 computed tomography (CT) and magnetic resonance imaging (MRI) examinations were performed in migraine patients. In that series, the yield of intracranial pathology was 0.4%; 3 tumors and 1 AVM. Still, in one of these patients the detected abnormalities were felt not to be related to the presence of migraine, and in two other patients the migraine was accompanied by a seizure disorder, thus increasing the a priori chance of finding a structural abnormality in the brain. Since Frishberg's paper, new large-scale studies addressing the yield of intracranial pathology using neuroimaging in headache patients have been published (94-97). Two of these studies evaluated pediatric populations (94,95). Weber-Bingol et al. investigated 429 consecutive patients, aged 5 to 18 years, diagnosed with migraine or tension-type headache (95). Although MRI revealed structural changes in 17.7% of these patients, none of these changes was considered to be related to the patient's headache. In another study on a pediatric population (3-18 years), CT and MRI were performed in 78 predominantly migraine and chronic TTH patients (94). In this study neuroimaging was performed for a variety of reasons, such as atypical headache pattern, presence of neurological abnormalities during the headache, general symptoms, or fear of brain tumor. Intracranial abnormalities were found in only 4 patients, and, again, these findings were judged to be unrelated to the headache. Akpek et al. reported a study of 592 neurologically normal patients with various types of headache who were submitted to CT (96). In their study, no intracranial lesions were found that were felt to be responsible for the headache or that changed the clinical or therapeutic approach. Finally, Dumas et al. reported a series of 402 CT scans (mostly enhanced with contrast agents) that were performed in patients with chronic unspecified headache and a normal neurological examination (97). On four scans significant lesions were found: osteoma in two cases, one low-grade glioma, and one aneurysm. These authors stated that the detection rate of CT abnormalities in patients with chronic headache is similar to that expected in the general population, provided the neurological findings are normal.

**Single-photon emission computed tomography (SPECT) and positron emission tomography (PET)**

**SPECT and PET in headache patients**

Regional cerebral blood flow (rCBF) has been the key parameter measured in the majority of SPECT and PET imaging studies in headache patients. rCBF recordings are robust and there is a substantial body of evidence in this field based on rCBF findings in headache patients examined using the older, stationary detector methods, e.g., the intra-carotid method (98,99). Thus, experience with rCBF in headache patients, and particularly in migraine, dates back more than 25 years. In most instances the SPECT and PET investigations have confirmed previous findings, but the modern methods have also added new information (100). Only in very few studies have other parameters, such as oxygen metabolism, glucose-metabolism or receptor ligand binding been measured.

**Tension-type headache**

The literature is sparse and no specific rCBF or metabolic alterations related specifically to the headache or occurring during the interictal phase have been reported. General arousal and pain can affect the global flow and metabolism in both the positive and negative directions and should be considered in future studies. This is an unspecific reaction that might be seen in other types of pain as well as in tension-type headache.

**Migraine without aura**

No specific cortical rCBF changes occur during attacks (101,102), although there could occur unspecific changes related to general arousal and pain as discussed above. These rCBF changes could take the form of either increased or decreased activity.

**Migraine with aura**

During a migraine with aura attack, focal blood flow changes occur, beginning just prior to the start of the aura symptoms and evolving over the following hours. Typically, a focal hypoperfusion is seen in the posterior aspect of one hemisphere, usually around the watershed region between the posterior and middle cerebral artery (MCA) supply territories (98). This hypoperfusion can involve larger parts of the hemisphere or in some cases appear only in the frontal region, but it is always confined to one hemisphere. The focal hypoperfusion outlasts the aura phase and persists into the subsequent headache phase followed by a gradual return to normal perfusion levels. Hours later, by the end of the headache phase or when the headache has resolved, the previously hypoperfused region becomes relatively hyperemic – so-called ‘tardive hyperemia’ (103). If the method allows frequent, repeated rCBF studies it is possible to show that the initial hypoperfused region increases in size during the aura phase – ‘spreading oligemia’ (104). As the spreading hypoperfusion evolves over a period of 20 to 40 minutes one should perform measurements at intervals of a few minutes in order to visualize the dynamic changes. Only the PET (and functional magnetic resonance imaging [fMRI]) method but not the SPECT method will allow this (105).

**Atypical aura-like or migraine-like attacks**

rCBF changes similar to those seen during migraine with aura have been reported in borderline cases. This finding has been reported in patients with severe aura symptoms mimicking transient ischemic attacks (TIAs) and in hemiplegic migraine (106,107).
Interictal images in migraine

With the exception of a few rare cases of patients developing infarctions, the rCBF pattern during the interictal phase is not normally characterized by severe focal changes. However, it is quite common for rCBF images to display slight asymmetries interictally (108). These have been attributed to a supposed unstable or fluctuating rCBF regulation in migraine patients. These ‘patchy’ rCBF patterns have been described in approximately 50% of migraine patients predominantly suffering from both migraine with and migraine without aura.

Cluster headache

There are diverging reports on functional imaging findings in cluster headache patients (109-113). Most findings are negative, i.e., no specific blood flow changes in cluster headache patients during or outside attacks. A few studies have shown slight frontal hyperfusion in some patients. A recent PET study has shown increased rCBF in deeper structures, like the hypothalamus, which was attributed to pain-induced neuronal activation rather than direct vascular involvement (114). On the basis of the literature, it can be concluded that no specific diagnostic rCBF changes occur in cluster headache patients, either interictally or during attacks.

Symptomatic (secondary) headache

In patients with headache secondary to other medical conditions there are no specific rCBF alterations that are related to the headache. However, marked rCBF and metabolic changes attributable to the primary condition, e.g., stroke, TIAs, trauma, neuro-infection, subarachnoid hemorrhage and AVMs, are often present. AVMs often present with migraine with aura-like symptoms as the first sign. It is likely that AVMs can trigger true migraine attacks.

Headache in children

Generally, the findings in children are similar to those in adults (115-117). However, there are only a few reports of studies in children, and reports on pre-school age children are particularly scarce.

Transcranial Doppler (TCD)

Migraine without aura

Migraine without aura attacks appear to be accompanied by a decrease in blood velocity in the MCA on the headache side during attacks (65,99). Other authors have, however, reported a generalized increase in blood velocities in the basal intracranial arteries during attacks (118) or no significant change (119,120). Between attacks MCA velocities are normal and symmetrical (66,99,119,121).

Migraine with aura

A decrease in MCA blood velocities on the headache side has generally been found during migraine with aura attacks (99). Some authors have found a bilateral decrease (118,122,123), whereas others have found no significant MCA blood velocity changes during attacks (119). Friberg et al. (124) carried out combined TCD and rCBF measurements and did not find significant changes in rCBF in the MCA perfusion territory on the symptomatic (headache) side. A decrease in MCA velocities with no change in rCBF in the MCA perfusion territory suggests MCA dilatation during attacks. The MCA dilatation was also seen in attacks without aura and is most likely related to the pain mechanism itself and not to aura symptoms. The unilateral MCA dilatation returned to normal after treatment with sumatriptan. MCA velocities remain normal (121) or show bilateral increases (121) outside attacks.

Cluster headache

Cluster headache attacks may be accompanied by a bilateral decrease in MCA blood velocities, which is more pronounced on the symptomatic side (110,111,124). Dahl et al. (110) carried out combined TCD and rCBF measurements and did not find significant rCBF changes in the perfusion territories of the MCAs. These findings, combined with the TCD measurements, suggest a bilateral dilatation of the MCAs during attacks which is more pronounced on the symptomatic side. Further, there is evidence that MCA velocities may be higher on the symptomatic side outside cluster periods (110). TCD results in other primary headaches are sparse and inconclusive.

Recent advances and perspectives in neurophysiological investigations in headache

Migraine is a paroxysmal disorder characterized by an attack threshold that varies across the interictal interval. The attack preparation that occurs during the interictal period is reflected in subtle functional abnormalities, which are strictly disease-related and not detectable in non-migraine subjects. Peculiarly, these abnormalities normalize as the migraine attack progresses. During the subsequent interictal period, these central nervous system changes once more appear and gradually develop, in preparation for the next migraine attack. The main contribution of evoked potential studies conducted in the field of primary headache, especially migraine, has been to show that these interictal abnormalities exist. In fact, the most consistent finding yielded by evoked potential studies in migraine is the lack of habituation of evoked responses. Several studies on PRVEPs have shown that N1P1 and P1N2 amplitudes tend to remain unchanged or even increase during sustained visual stimulation at 3.1 Hz, while in healthy controls the evoked responses tend to decline with the persistence of the repetitive stimulation (i.e., showing habituation). The degree of PRVEP habituation has been found to be negatively correlated with the low amplitude in the first block of averaged responses (126). This may suggest that the abnormal response potentiation in migraine may be due to a reduced precactivation level of the sensitive brain in migraine, which offers a large...
suprathreshold range of activation. VEP habituation may depend on check size and on the attack-interval cycle (127). Further evidence of altered central information processing in migraine comes from a recent study on gating of middle-latency auditory evoked cortical potentials (128). This study shows a markedly lower suppression of the middle-latency P50 component of the auditory cortical response to the second of two homologous auditory stimuli. According to the authors, the sensory gating impairment and the dishabituation pattern observed after sustained stimulation are underpinned by a single dysfunction at pre-cortical level, possibly a hypofunctioning of the cortico-subcortical monoaminergic system, as the reduced cortical preactivation level may suggest. Indeed, a dishabituation pattern has been shown not only in cortical responses, as seen above, but also in the brainstem and cortical components of somatosenory-evoked potentials. The cervical component N13 showed a significant potentiation in the second of four blocks of 100 responses at 3Hz stimulation frequency (129) and R2 and R3 blink reflex components showed reduced habituation of the fifth response when evaluated during repetitive stimulation at increasing interstimulus intervals (ISIs) (130). These data suggest a more generalized information processing dysfunction in migraine, not limited to cortical level. Dishabituation shown in evoked potentials could represent a phenotypic marker in a large subgroup of migraine sufferers. The evidence of a familial – and possibly genetic – character of the dishabituation pattern points to a phenotypic-genotypic correlation, which represents a challenge for future research (131). These electrophysiological data further support the view that migraine is not simply a trigeminovascular disorder, but a complex disease characterized by central disruption of sensory processing and cortical disinhibitory. A polysomnographic study of eight migraine subjects suffering from nocturnal or early morning attacks has revealed a trend of lower total rapid eye movement density and number of EEG arousals, as well as a significant decrease in spectrum power in slow-wave sleep (132). In the limited number of subjects investigated, these findings suggest, once more, a decrease in cortical activation the night before an attack, which might result from a temporary impairment of the cerebral cholinergic input and/or the aminergic drive and, consequently, in the transition from the interictal to the ictal cortical state. The same temporal pre-ictal transition, clinically reflected in prodromal phenomena and described as irritability, drowsiness etc., has been shown as dynamic changes occurring in the habituation pattern and contingent negative variation (CNV) amplitude in the interval between attacks, which abruptly normalize as the attack occurs. The CNV is an event-related slow cortical potential evoked by a reaction-time task stimulation paradigm. Migraine without aura subjects during the interval between attacks show a progressively increasing CNV amplitude, especially of the early component, regarded as an index of central noradrenergic hyperactivity, which is restored to normal during the migraine attack and by beta-blocker prophylactic treatments (133). This higher CNV amplitude has been demonstrated to be partly sustained by a lack of habituation across sequential blocks of averaged trials. Even though already shown in exogenous, visual and auditory, cortical evoked potentials (134), the dishabituation pattern also demonstrated in event-related potentials, which reflect cognitive processing and a much more complex neuronal network system, seems to support the view of a general abnormality of sensory information processing in migraine. Although other authors failed to confirm differences in CNV amplitude versus healthy controls, the dishabituation pattern was also found in 60% of children and 30% of adult controls, indicating that habituation in CNV trials is not specific for migraine, but a developmental feature of information processing and possibly a predisposing factor for the development of migraine (135). One entirely original and particularly interesting approach to the neurophysiology of migraine has been the study of chemo-sensory evoked potentials with the use of an olfactory stimulator (136). Using a pure trigeminal stimulant, CO2, or a pure olfactory stimulant, H2S, the authors showed increased amplitudes and reduced latencies to the CO2 stimulus, suggesting hyperexcitability of the trigeminal system, while the responses to H2S were reduced, suggesting olfactory hypexcitability.

**Blink reflex**

Changes in cortical excitability over time and functional neuroimaging studies both point to a dysfunction at brainstem level. Electrophysiological tests of the trigemino facial system by means of BR techniques are valuable tools for exploring nociceptive modulatory pathways. As seen in the studies mentioned earlier, the BR has yielded contrasting data in migraine. In an early study of the BR in migraine, an increased R2 latency was reported (51) suggesting a brainstem dysfunction, but this finding has not been replicated in several studies conducted since then (52,137,138). Only during the headache phase have lower amplitude and area of the R2 responses been found bilaterally (137). Studies on the recovery cycle of the BR in migraine patients with ISIs of 100, 200, 300 and 500 ms, have shown no difference compared to controls (138). By contrast, a very recent study applied a new method for the selective activation of cutaneous nociceptive fibers (without recruiting the non-nociceptive A-Beta fibers) by means of a novel concentric electrode to elicit the BR (139). The examinations were performed both with the novel and the standard procedures, during and two hours after treatment of a migraine attack, and the results compared to values obtained in the headache-free interval. These authors found a shortening of R2 latencies and an increased reflex integral (area under the curve [AUC]) during the acute migraine episode, not shown by the standard procedure. The blink R2 responses were markedly facilitated bilaterally, but mostly on the pain side, compared to the headache-free interval. Symptomatic treatment with zolmitriptan or lysine acetylsalicylate partially reversed these changes with normalization still present interictally. The authors considered their results suggestive of a temporary sensi-
zation of central trigeminal neurons occurring during acute migraine attacks, since facilitated nociception-specific BR responses were found and are in keeping with the clinical observation of the development of cutaneous allodynia during an attack (140). Similarly, the R3 ultralate component of the BR has been found to have an increased area on the pain side during the migraine attack, which is reversed by zolmitriptan but not sumatriptan (141).

In another study, the same authors also reported reduced R3 thresholds interictically both in cluster headache and migraine patients, suggestive of a permanent derangement of the descending pain control system and/or sensitization of the trigeminal network by the concomitant neurogenic inflammation. Unfortunately, since the nature of the R3 component is still debated and not considered specifically nociceptive, these data cannot be interpreted unequivocally. The recovery curve of the blink R2 component has been performed in patients during cluster period. The data obtained add further support to the hypothesis of hyperexcitability of the central loop of the BR (53). The authors assessed the effect of conditioning stimuli on the R2, both at trigeminal and peripheral level, with paired stimuli at increasing ISIs. They showed a markedly enhanced recovery curve compared to controls with both peripheral and segmental conditioning stimuli. With the segmental conditioning the R2 recovered even more rapidly on the symptomatic side, suggesting unilateral sensitization of the trigeminal pathway. Another author reported only R2 amplitude asymmetry in cluster headache patients (142), but healthy controls were not investigated.

**Corneal reflex in primary headaches**

A reduced threshold of the electrically-induced CR has been found in cluster headache patients during the active period, with lower values on the pain side (54) compared both with healthy controls and, in the same subjects, with the remission phase. These data have been interpreted as suggestive of enhanced trigeminal nociceptive neuron excitability, possibly concomitant to derangement of integrative, nociceptive and autonomic, functions of the pain-control system during bouts. More recently, this electrophysiological method has been applied to a migraine sample including a subgroup of migraine patients with strictly unilateral pain attacks (143). The results showed a reduction of pain and reflex thresholds in migraine patients between attacks compared to controls. The lowest values were found on the symptomatic side in patients suffering from side-locked pain attacks. Because of the bilateral location of the abnormalities, even in the unilateral headache subgroup, it has been hypothesized that a centrally-located dysfunction in the nociceptive modulatory pathway emerges in migraine as a result of neuroplastic changes that occur in response to persistent input of pain signals.

Based on the hypothesis of trigeminal sensitization, one group very recently studied the habituation of the BR in 19 patients suffering from cluster headache (144). The habituation pattern of the R2 component of the BR was explored in 19 drug-free episodic cluster headache patients in an active period by means of increasing frequency of stimulation (0.2, 0.3, 0.5, 0.7 and 1 Hz) and the results were compared with those of 20 healthy volunteers. The habituation was computed as percent decrement of the second and third blocks of 5 responses compared with the first block. The statistical analysis showed a significant difference in the adaptation of the R2 response at high frequency of stimulation, i.e., R2 habituation, with a reduced percent decrement at 0.7 and 1 Hz on both (symptomatic and non-symptomatic) sides in cluster headache patients versus controls. These findings are not comparable to the cortical evoked response findings observed in migraine, since this study dealt with an exteroceptive brainstem reflex. These data seem to point more to a sensitization of trigeminal pathways rather than to dishabituation in sensory processing. They suggest that during active periods of cluster headache a central derangement in the pain control system may favor a lack of habituation of the BR as an expression of enhanced neuronal excitability at brainstem level, with amplified trigeminal nociception. Indeed, the extensive release of neuroactive molecules (substance P, NO) observed during cluster pain attacks may affect the modulation and sensitivity to pain via NMDA-mediated mechanisms (144).

**Single fiber-EMG studies**

Application of the single fiber-EMG technique in a subgroup of migraine with aura patients has revealed subclinical impairment of neuromuscular transmission compared with healthy controls without a personal or family history of headache (128). These abnormalities were found to be significantly correlated with the complexity and duration of aura symptoms, being prominent in subjects with aura characterized by sensorimotor symptoms, language disturbances and loss of balance.

**Recent advances and perspectives in the field of neuroimaging and neurosonology research in headache**

**Perfusion-weighted imaging MRI**

**Migraine with aura**

During a spontaneous migraine with visual aura attack changes in blood flow are observed in the contralateral visual cortex, while the focal neurological symptoms are present, and persist into the headache phase (145,146). Semi-quantitative blood flow measurements show a decrease at first examination approximately 30 minutes after onset of visual symptoms. At this time rCBF was reduced by 27%, regional cerebral blood volume (rCBV) was reduced by 15%, and mean transit time was increased by 32% in the visual cortex contralateral to the affected visual field (146). The focal hypoperfusion slowly returns to interictal baseline values more than 1 hour after resolution of the aura symptoms. At later time points, a hyperemic phase has, in some cases, been documented in the same regions that showed the hypoperfusion. Thus, the events previously found with the intra-carotid and SPECT rCBF methods (98,99,101,103,104) have now been confirmed with the IMRI methods. The perfusion deficits...
showing a reduction in water diffusion during a pro-
changes (145). However, Chabriat et al. (150) succeeded
in patients suffering from spontaneous migraine with vi-
Migraine with aura
Diffusion-weighted imaging (DWI)
In patients suffering from spontaneous migraine with vi-
ual aura and in post-aura scans of these same patients,
was observed. At 3 months after onset, the diffusion images normalized. Methodological issues
artificial of the arterial puncture.
An X-133 kept in all coordinates, and the diffusion reductions
Aura

Migraine with aura
Blood Oxygenation Level Dependent (BOLD)
Migraine with aura

Atypical aura-like or migraine-like attacks
A typical case of pseudomigraine with temporary neuro-
neuronal dysfunction (147-149). A DWI defect has been demonstrated in only
these calculated values are above those associated with

Hemiplegic migraine
Multiple single case reports of hemiplegic migraine have
evolve over time with maximum deficit during aura (10%
to 37% below normal as estimated from fMRI recordings).
Hemiplegic migraine
Studies performed across a wide range of time points
have failed to show any perfusion changes in either the
cortex or the brainstem (146). One subject who was
studied during the migraine aura and exhibited the typi-
cal perfusion changes, was also studied during a typical
migraine without aura attack; as was expected, during
the latter attack no cerebral blood flow (CBF) changes
were evident. This case clearly illustrates that perfusion
abnormalities are a fingerprint of migraine aura symp-
toms and not related to the migraine headache itself.

Diffusion-weighted imaging (DWI)
Migraine with aura
In patients suffering from spontaneous migraine with vi-

Functional Neurology 2003; 18(3): 127-144
starts at the primary visual cortex, spreading into contiguous occipital cortex bilaterally at a rate of 4.1±1.3 mm/min. These findings resemble those of the PET studies by showing spread of the signal over both hemispheres in migraine without aura (105). Changes are not only observed over the cortex but also in the substantia nigra and red nucleus bilaterally. The MR signal returned to baseline despite persistence of headache, reflecting how cortical events can activate subcortical centers that are possibly involved in nociception and associated symptoms of the migraine attack (155). These BOLD data suggest that an electrophysiological event, such as CSD, not only could be associated with the migraine aura but also could play a role in migraine without aura, and show for the first time a clear hyperemic phase preceding the hypoperfusion.

**Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT)**

A single case of SUNCT imaged during several paroxysms of pain showed activation in typical pain centers such as the insula, thalamus and gyrus cinguli (156). The activation observed in the ipsilateral hypothalamus resembles that observed in cluster headache. From the viewpoint of efforts to explain the pathogenesis of paroxysmal pain, the hypothalamus is an important center, being known to participate in the descending control of pain through its connections to the periaud-duc tial gray matter, and to control circadian rhythm. The hypothalamus also has connections with the nucleus of the solitary tract, thus helping to explain some clinical autonomic disturbances related to vagal (parasympa-thetic) functions. The activation in the ipsilateral hypothalamus per se does not reveal a functional abnormality since it may be activated in response to pain, but the failure of the contralateral hypothalamus to show activation may reflect the functional abnormality.

**Magnetic resonance spectroscopy (MRS)**

**Migraine with and without aura**

Spectroscopy has been used to look for evidence of abnormal energy metabolism in the brains of migraineurs both interictally and during attacks. Magnesium levels are reduced in posterior regions of the brain in hemiplegic migraine but not in other types of migraine with or without aura either ictal or interictal (157). 1H-MRS during photic stimulation showed a 6%-10% decrease in N-acetyl aspartate, creatine, and choline stimulation in migraine with aura but not in migraine without aura outside an attack. These data taken together suggest altered energy metabolism and mitochondrial dysfunction in migraine patients (158). The neurons and glia of migraineurs may have low energy reserves and thus less ability to tolerate the demands of increased energy expenditure than those of normal individuals, thus lowering their threshold for migraine attacks.

**Cluster headache**

A defect in brain energy metabolism (decrease in high energy phosphates) has been found during and after a cluster period, although the patients were not studied during an attack (159). The changes resembled those found previously in migraine patients thus suggesting a similar biochemical/metabolic abnormality in both headache disorders, perhaps a mitochondrial dysfunction.

**MRI and brain iron levels**

Specific MRI methods (transverse relaxation rates) are able to quantify brain iron levels (non-heme iron), particularly in gray matter regions. These are of great interest since they can provide information on the pathogenesis and progression of different diseases.

**Episodic migraine and chronic daily headache**

In the periauduc tual gray matter (PAG), a positive correlation is observed between duration of illness and transverse relaxation rate (increased iron deposition) in the episodic migraine and chronic daily headache groups (160). This is interpreted as a selective and persistent impairment in iron homeostasis in the PAG in episodic migraine and chronic daily headache, most likely as a result of repeated migraine attacks and, hence, might explain the transformation from episodic to chronic daily pain. The implication that repeated attacks of migraine might lead to structural brain damage may demand further study.

**Magnetoencephalography (MEG)**

Magnetoencephalography (MEG) is a technique able to measure magnetic fields produced by electrical events in the brain. Although preliminary studies in migraine patients during visual aura failed to demonstrate clearly MEG changes compatible with cortical spreading depression, a recent study succeeded in establishing such a relationship (161). Complex direct current magnetoencephalographic shifts were observed in spontaneous and visually induced migraine patients, but not in controls. Similar findings have been observed in MEG studies in experimental animals during cortical spreading depression, where magnetic field shifts propagate along the gyrencephalic cortex (162).

**Transcranial magnetic stimulation (TMS)**

Transcranial magnetic stimulation (TMS) is the application of magnetic fields of increasing intensity in order to evaluate the excitability of the cortex. Interictal studies in migraine with and without aura have given conflicting results. While one argument, on the basis of the lower threshold needed to induce phosphenes and the ease with which headaches could be triggered by visual stimulation, is that the occipital cortex of migraineurs is hyperexcitable (163-167), another group demonstrated the exact opposite (168). A significantly lower prevalence of phosphenes in migraine with aura was observed after occipital TMS. There are methodological differences between these studies, such as the size and positioning of the stimulator, which makes attempts to reconcile these results difficult. Motor evoked potentials in hemiplegic migraine, mi-
graine with and migraine without aura did not show differences between patient migraine groups and controls, therefore failing to show hyperexcitability (168,169). A recent study comparing cortical excitability in chronic migraine and migraine without aura confirmed previous results, but revealed that the duration of the cortical silent period was longer in chronic migraine patients (170). More studies are needed to establish whether this finding is related to pathogenic changes secondary to transformation into chronic migraine.

**Positron emission tomography**

**Migraine with aura**

In attacks provoked by ingestion of red wine, no statistically significant changes in rCBF were detected during the ongoing aura, whereas during the headache phase in both migraine with and without aura, a 23% decrease in the blood flow and 22.5% decrease in metabolism in the primary visual cortex were observed (171). These results are thus at variance with previous findings for migraine aura since they failed to confirm a decrease in rCBF in the posterior regions of the brain. They do report, on a case-by-case basis, decreases in blood flow in different brain regions that unfortunately do not correspond to the symptoms described.

**Migraine without aura**

A first PET cerebral blood flow study during a migraine attack revealed bilateral spreading hypoperfusion (105). The maximum drop in blood flow was estimated to be about 40%. It is important to note that the hypoperfusion started in the visual associative cortex (Brodmann’s areas 18 and 19) and progressed over time across vascular and anatomical boundaries. This is the first report of migraine without aura associated with a spreading hypoperfusion affecting both hemispheres, an important finding given that a spreading hypoperfusion affecting only one hemisphere had previously been clearly documented only during migraine with aura. This case also illustrates the possibility, in migraine without aura, of subclinical spreading blood flow changes resembling CSD that do not reach the threshold for perceptual deficits. Subsequent studies have provided new information on other structures involved in the pathophysiology of migraine. Spontaneous migraine without aura attacks studied within 6 hours of onset showed a significant local increase in blood flow in the cingulate, auditory and visual association cortices, structures well known to be activated during pain and not considered specific to migraine pathogenesis. The most important finding was an increase in rCBF (+11%) in medial brainstem structures, mainly contralateral to the headache side. After patients were treated with a subcutaneous injection of sumatriptan and relief of the headache and accompanying phono- and photophobia had been achieved, only the blood flow increase in the brainstem persisted. Although the resolution capacity of PET does not allow the rCBF changes to be attributed to specific nuclei, the activation pattern appears in a region of the brainstem important in nociceptive and vascular control (most likely locus ceruleus and dorsal raphe nucleus). The persistent increase in rCBF, even after the relief of symptoms, underlines the importance of these structures in the pathogenesis of migraine. It is, however, not clear whether these brainstem nuclei serve as a migraine generator, participate in modifying the threshold for neuronal activation, or are part of the neuronal system that terminates an attack. Recently, Bahra et al. (172) reported rostral brainstem activation in a single patient. Although the activation did not correspond to exactly the same brainstem structures previously reported, it confirms the relevance of the brainstem in the pathogenesis of migraine compared with other headache syndromes.

A separate cerebral blood flow study in migraine without aura patients conducted within 13 hours (range 3.8 hours to 24.5 hours) of onset of a spontaneous headache showed global decreases in CBF (-9.9%) and cerebral blood volume (CBV) (-5.2%) rather than areas of focal increase in CBF (173). No relationship was observed between the time from onset of the headache and the changes in blood flow, and no significant changes were observed in oxygen metabolism or oxygen extraction. It should be emphasized that the study was not designed to detect spreading of the hypoperfusion through the course of the attack and did not focus on the brainstem.

**Cluster headache**

Ictal studies during nitroglycerin-induced attacks have shown significant increases in blood flow in the ipsilateral hypothalamus and basal ganglia, contralateral posterior thalamus, and bilaterally in the cavernous sinus, cingulate cortex and insula (114). The increased blood flow observed in the cavernous sinus was found by magnetic resonance angiography to be secondary to internal carotid vasodilatation (174). Although hypothalamic activation during pain conditions has previously been reported (175), within headache syndromes it has only been observed in cluster headache and SUNCT.

Further evidence in favor of hypothalamic involvement was provided by anatomical MRI of cluster patients and application of voxel-based morphometry, providing an objective and automated method of analyzing changes in brain structure (156). With this technique, an increase in gray matter volume in the hypothalamus was observed ipsilateral to the pain; unfortunately, the nature of this volume change is not known.

**Transcranial Doppler (TCD)**

**Migraine without aura**

Recent TCD studies have tried to clarify the dynamic pattern of the cerebrovascular response in migraineurs by using visual stimulation (176). The middle cerebral artery (MCA) of migraineurs exhibited a steady increase in blood velocity (CBVe) during the stimulation, while normal subjects showed habituation of the CBVe response. The lack of habituation in migraineurs was more pronounced across patients with a high attack frequency (> or = 4 per month) compared with migraineurs with a low attack frequency (< 4 per month). In the posterior cerebral artery, compared with normal subjects,
migraineurs showed stronger CBVe changes at the beginning and after the end of stimulation, with a slower decline to baseline. This finding confirms the habituation demonstrated by means of other functional techniques.

One way of studying autonomic activity is to measure the spontaneous oscillations in CBVe (177). There is experimental evidence that B waves are generated by brainstem nuclei, while Mayer waves represent peripheral autonomic activity. The coefficient of variation of B waves was found to be higher in migraine patients indicating an increase in the activity of brainstem nuclei. Patients with chronic tension-type headache had lower Mayer wave activity values in comparison with normal controls, considered a sign of impaired activity in sympathetic cardiovascular neurons (177). Another way of testing cerebrovascular reactivity is by means of hypercapnia, using the breath-holding index. Interictal studies in migraineurs showed an exaggerated reactivity to hypercapnia rather than an increased vascular tone, as was previously assumed (178). This hyperreactivity is reversed after prophylactic treatment with flunarizine (179).

**Migraine with aura**

TCD has been used to show the higher prevalence of the patent foramen ovale in migraine with aura patients. This is believed to be a potential source of microemboli, which are probably responsible for the focal neurological symptoms (180).

**Hemiplegic migraine**

A single case of hemiplegic migraine studied before and after verapamil treatment (5 mg iv) showed an initial vasospasm that was reversed by pharmacological treatment. The vascular changes correlated with the gradual resolution of the clinical deficit (181).

**Future research**

**EEG**

QEEG methods are generally preferred in scientific EEG studies. The reliability of each QEEG method needs to be established. The temporal relationship with the previous and next attacks seems to be important. More polygraphic studies on the relationship between EEG, hyperventilation, migraine and sleep are needed. The search for improved photic driving protocols should continue.

Magnetoeencephalographic (MEG) studies of migraine patients during headache have demonstrated either slow wave-shifts (similar to those observed in animals with spreading depression) or suppression of activity (182). The identification and elimination of artifacts constitute a major challenge in MEG research (182,183). MEG is expensive and not generally available for the diagnosis of individual patients.

**Evoked potentials**

Visual evoked potentials (VEPs) offer several exciting prospects in migraine research. Primarily, they can help to further understanding of the pathophysiology of the underlying disorder. First, however, terminological confusion will have to be cleared up. The word ‘hyperexcitability’ has been used by some to express the fact that responses were larger in migraine than in control groups, whereas others are skeptical, because they argue that the basic disorder is a lack of inhibition, rather than hyperexcitability. We propose using the word ‘reactivity’ to describe the measured signals. ‘Increased reactivity’ would then simply mean that responses are larger than in a control group. The terms ‘hyperexcitability’ and ‘impaired inhibition’ could then be used to describe two mechanisms that may explain why the responses were larger. Understood in the latter sense, presently available evidence points toward impaired inhibition in migraine.

The second aspect concerns serial recordings: presently there is no way of predicting an attack, one just has to wait for it to occur. There is evidence that cortical excitability changes at least one day, or more, before an attack. If this aspect can be measured reliably, the genesis of attacks can be studied. Prophylactic drug studies could benefit considerably from the possibility of studying sub-threshold migraine tendencies.

**Reflex responses**

Trigeminal pain control system involvement seems to play an important role in the pathogenesis of primary headache. The nociceptive reflex abnormalities described in primary headache patients support this hypothesis. Further studies using the NFR method in large populations with differing disease severity could confirm whether or not this neurophysiological test is a useful marker. The administration of drugs acting on specific receptor populations could provide information on the pathogenetic role of the neurotransmitters, the mechanism of the drug and the profile of responders.

**Autonomic tests**

Most studies have failed to formulate sound and testable hypotheses regarding the involvement of the autonomic nervous system (ANS) in headache (184). Any hypothesis must start with clinical observations, but also break down the putative mechanisms behind these observations into component parts that are testable in animal models in vivo and in vitro. The mechanism of headache as such (e.g., migraine or cluster headache) cannot be tested in animal or human models. Similarly, reflex sympathetic dystrophy (RSD, complex regional painful syndrome type I) cannot be tested in animal models but only components of RSD, such as sympathetically-maintained pain, swelling, trophic changes, or motor deficit mechanisms. It is equally clear that any progress in connection with the involvement of the ANS in the generation of headache can only be expected from basic research using animal models in conjunction with research in humans and detailed investigations of the clinical phenomena (185-188). Furthermore, the largely negative results regarding the involvement of the ANS in headache (e.g., migraine) (65,66) do not exclude that specific autonomic systems, which elude the testing procedures, are involved in the generation of pain. Finally it is possible that the ANS (e.g., the sympathetic system and the sympatho-adrenal system) is...
involved in the generation of pain, including different types of headache, through mechanisms entirely different from those hitherto described (189,190).

Evaluation of pericranial muscle tenderness (with special reference to tension-type headache)

In future studies the pathophysiological significance of increased tenderness and hardness of pericranial muscles should be elucidated. It is especially important to clarify whether these findings are a cause or an effect of the pain. Valid experimental models of chronic myofascial pain need to be developed and used in pathophysiological and pharmacological studies.

Functional brain imaging: SPECT, PET and fMRI

Functional neuroimaging methods still have vast potential in future headache research, particularly in the investigation of migraine pathophysiology. The PET and SPECT techniques offer possibilities for in vivo imaging of neuroreceptors (191). The in vivo receptor technique does not only offer possibilities for the radio-labeling of pharmaceutical compounds with potential for treatment; using well-known radio labeled receptor ligands it is also possible to quantify the displacement from the receptors by use of pharmacologically active doses of non-labeled compounds. Further PET and SPECT studies are also warranted in order to re-visit the basic questions of whether the migraine-associated blood flow changes are of primary vascular or neuronal origin. We still need more information on regional changes in brain metabolism during aura and headache. Also, further studies are needed to confirm recent findings, i.e., the suggestion of a focal migraine ‘generator’ (192). In headache research the fMRI technique has been applied only in a few recent studies. Basically, preliminary studies have confirmed the findings of previous regional cerebral blood flow studies (145,153,154). Because the fMRI technique offers fast imaging with high resolution and because the technique is widespread it will yield new knowledge on headache pathophysiology within the next few years.

Appendix - Abbreviations used in this review

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AEP</td>
<td>auditory evoked potential</td>
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<tr>
<td>ANS</td>
<td>autonomic nervous system</td>
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<td>AVM</td>
<td>arterovenous malformation</td>
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<td>BOLD</td>
<td>blood oxygenation level dependent</td>
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<td>BR</td>
<td>blink reflex</td>
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<tr>
<td>CBF</td>
<td>cerebral blood flow</td>
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<td>CBV</td>
<td>cerebral blood volume</td>
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<tr>
<td>CBVe</td>
<td>cerebral blood velocity</td>
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<tr>
<td>CR</td>
<td>corneal reflex</td>
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<td>CEOP</td>
<td>childhood epilepsy with occipital paroxysms</td>
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<td>CNV</td>
<td>contingent negative variation</td>
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<td>CSD</td>
<td>cortical spreading depression</td>
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<td>CT</td>
<td>computed tomography</td>
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<td>DWI</td>
<td>diffusion-weighted imaging</td>
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<tr>
<td>EEG</td>
<td>electroencephalography/encephalogram/en-cephalographic</td>
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<td>EMG</td>
<td>electro-myography/myographic</td>
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<td>ES2</td>
<td>exteroceptive suppression (second component)</td>
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<td>fMRI</td>
<td>functional magnetic resonance imaging</td>
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<tr>
<td>ISIs</td>
<td>interstimulus intervals</td>
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<td>MCA</td>
<td>middle cerebral artery</td>
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<td>MEG</td>
<td>magneto-encephalogram/encephalography/en-cephalographic</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>NFR</td>
<td>nociceptive flexion reflex</td>
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<td>PAG</td>
<td>periaqueductal gray matter</td>
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<td>PET</td>
<td>positron emission tomography</td>
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<td>PPT/s</td>
<td>pressure pain threshold/s</td>
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<td>PRVEP/s</td>
<td>pattern reversal visual evoked potential/s</td>
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<tr>
<td>OEEG</td>
<td>quantitative electroencephalography</td>
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<tr>
<td>rCBF</td>
<td>regional cerebral blood flow</td>
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<tr>
<td>rCBV</td>
<td>regional cerebral blood volume</td>
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<tr>
<td>RSD</td>
<td>reflex sympathetic dystrophy</td>
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<td>R1</td>
<td>first component of the blink reflex</td>
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<tr>
<td>R2</td>
<td>second component of the blink reflex</td>
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<tr>
<td>R3</td>
<td>third component of the blink reflex</td>
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<tr>
<td>RIII</td>
<td>late component of nociceptive flexion reflex at lower limb</td>
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<td>SPECT</td>
<td>single-photon emission computed tomography</td>
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<td>SUNCT</td>
<td>short-lasting unilateral neuralgiform headache with conjunctival injection and tearing</td>
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<td>TCD</td>
<td>transcranial Doppler</td>
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<td>TMS</td>
<td>transcranial magnetic stimulation</td>
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<td>TAs</td>
<td>transient ischemic attacks</td>
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<td>VEP/s</td>
<td>visual evoked potential/s</td>
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