Autonomic asymmetry in migraine: augmented parasympathetic activation in left unilateral migraineurs

Yudith Avnon,1,2 Meir Nitzan,3 Elliot Sprecher,1 Zeev Rogowski2 and David Yarnitsky1,2

1Department of Neurology, Rambam Medical Center, 2Faculty of Medicine, Technion, Haifa and 3Department of Applied Physics/Electro-optics, Jerusalem College of Technology, Jerusalem, Israel

Summary
Brain autonomic control is asymmetrical, the left hemisphere affecting predominantly parasympathetic function and the right hemisphere affecting predominantly sympathetic function. It is not known whether the extent of autonomic activation is altered in migraine, although the fact that some migraineurs express parasympathetic features such as facial flushing, lacrimation and rhinorrhea might suggest increased parasympathetic activation. We instilled diluted soapy eyedrops and measured (i) the trigemino-parasympathetic reflex by the vasodilator response of forehead skin bilaterally using photoplethysmography; (ii) the somato-sympathetic reflex by vasoconstriction in the index finger; and (iii) heart rate response. We studied 14 left-sided and 15 right-sided unilateral migraineurs outside attacks. We found that left-side migraineurs had significantly higher bilateral parasympathetic vasodilatation, regardless of the stimulation or measurement side (+60.1 ± 6.4%) compared with right-side migraineurs (+41.9 ± 6.4%, P < 0.05). Sympathetic vasoconstriction, however, was similar for the two groups (left, −15.9 ± 4.2%; right, −17.7 ± 4.1%, NS). Bradycardia was significantly more pronounced for the left-side migraineurs (interbeat, RR interval increase of +6.2 ± 1.1% versus +3.1 ± 1.1%, P < 0.04). We conclude that unilateral left-side migraineurs have increased parasympathetic activation in response to pain compared with right-side migraineurs. Sympathetic responses were similar in the two groups and seemed not to be affected by migraine side. Since cranial parasympathetic activity induces cerebral vasodilatation, this augmentation might be an inherent part of the migraine pathophysiology in these patients.

Keywords: migraine; parasympathetic; brain asymmetry; photoplethysmography; trigemino-parasympathetic reflex

Abbreviations: AM = amplitude; BL = baseline; BP = blood pressure; HF = high frequency; HR = heart rate; PPG = photoplethysmography


Introduction
Almost two centuries have passed since the first discovery of asymmetrical functions of the brain hemispheres by Dax (1836), who apparently preceded Broca (1865) in this discovery. It is now well recognized that the hemispheres not only differ in their mode of cognitive and emotion-related processing (Gainotti, 1972, 1983; Trevarthen, 1990), but that brain asymmetry is a multimodal phenomenon (Davidson, 1995), including a higher degree of somatosensory processing (Hari et al., 1997; Pauli et al., 1999; Coghill et al., 2001) and autonomic–physiologically related functions, such as cardiac control (Critchley et al., 2000).

The autonomic control of the heart is modulated by certain parts of the cerebral hemisphere, such as the insula, amygdala and lateral hypothalamus (Oppenheimer et al., 1992), the right hemisphere predominantly deals with the sympathetic system, while the left hemisphere deals with the parasympathetic system (Oppenheimer et al., 1992, 1996; Naver et al., 1996; Hilz et al., 2001). The two hemispheres maintain
a homeostatic balance between themselves in regulating the sympathetic, parasympathetic and baroreflex functions (Hilz et al., 2001). This equilibrium is compromised in patients with unilateral brain injury; autonomic asymmetry is evident in patients with intracranial tumours, cerebral trauma, encephalitis (Oppenheimer et al., 1990; Benarroch, 1997), unilateral temporal lobe epilepsy (Tinuper et al., 2001; Lee, 2002) and stroke (Lane et al., 1992; Koripelainen et al., 1993; Barron et al., 1994; Naver et al., 1996; Robinson et al., 1997; Tokgozoglu et al., 1999). Lateralization in cerebral cardiac control was also demonstrated in epilepsy patients undergoing inactivation procedure (Wada test) (Zamrini et al., 1990; Yoon et al., 1997; Hilz et al., 2001). In these studies, inactivation of the right hemisphere was associated with reduced sympathetic tone, manifested as decreased heart rate (HR) and blood pressure (BP) and increases in high frequency (HF) of HR and BP. Left hemisphere inactivation, on the other hand, was associated with reduced parasympathetic tone, manifested as increased HR and BP, increases in low frequency (LF) of HR and BP, and a shift in the sympathovagal balance towards sympathetic predominance manifested as increased LF/HF ratio of HR. The association of right cerebral hemisphere diseases with tachycardia mechanisms was investigated by Oppenheimer and colleagues, who demonstrated in humans that tachycardia and pressor responses were more often elicitable by stimulation of the right insular cortex, while stimulation of the left insular cortex was associated with bradycardia and depressor responses (Oppenheimer et al., 1992).

Migraine is a benign disease, with mostly unilateral headache, in which hemispheric arousal is documented during attacks, and to some extent also outside attacks (Welch et al., 1990; Schoenen, 1997, 1998; Aurora et al., 1998; Hassoing et al., 1999). Autonomic abnormalities can therefore be expected, and were indeed documented in these patients, including abnormal cardiovascular reflexes to haemodynamic challenges, altered heart rate variation, pupillary reactivity, vascular reactivity, electrodermal activity and altered catecholamine levels (Fié-Moller et al., 1978; Fanciullacci, 1979; Gotoh et al., 1984; Havanka-Kannainen, 1986; Havanka-Kannainen et al., 1986; Drummond, 1987, 1990, 1991, 1997; Boiardi et al., 1988; Mikamo et al., 1989; Appel et al., 1992; Martin et al., 1992; Pogacnik et al., 1993; Shechter et al., 2002). This is in addition to the commonly observed increased parasympathetic signs of lacrimation, facial flushing and rhinorrhea (International Headache Society Classification, 2004; Barbanti et al., 2002). The subgroup of strictly unilateral migraineurs is a natural clinical example of hemispheric imbalance (Crisp, 1981; Crisp et al., 1985, 1989; Gruzelier et al., 1987). However, there is little evidence that localization of pain to one side of the head is associated with disturbed functioning of the corresponding hemisphere. The trigemino-parasympathetic reflex (Drummond, 1992, 1995, 1997; Drummond and Lance, 1992; Avnon et al., 2003) was studied in the present work in unilateral migraineurs between attacks, measuring cutaneous vascular and systemic cardiovascular responses to painful stimulation with soapy eyedrops, in order to assess whether the painful hemisphere expresses an alteration in its relevant autonomic control.

**Method**

**Subjects**

Unilateral migraineurs were recruited through advertisements or were employees of the medical centre or the university. All patients signed informed consent, which was approved by the Ministry of Heath and Rambam Medical Center Human Subjects Committee. Thirty females who met the International Headache Society classification for migraine (1988) (and retrospectively also met the 2004 classification) with aura (eight patients) or without aura (21 patients), age range 21–50 years (mean 32.1 ± 8.7), were recruited after screening. Exclusion criteria were: (i) cardiovascular, renal or central and peripheral nervous system disorders, (ii) chronic use of medications for reasons other than migraine, (iii) use of prophylactic treatment for migraine; and (iv) eye and skin disorders. Subjects were questioned in detail to evaluate the migraine type, laterality of pain and the associated symptoms. Fifteen patients had headache restricted to the right side and 15 patients had a headache restricted to the left side. Some of these patients were participants in a previous study in our laboratory (Avnon et al., 2003). Photo-, phono- or osmophobia was present in all. Most patients suffered from nausea and vomiting during their attacks, and about half of them had increased skin sensitivity in the face and scalp during attacks. Headache frequency ranged between one and eight attacks per month (mean 2.8 ± 1.9) and the duration of attacks ranged between 4 h and 3–4 days (mean 28.9 ± 18.2 h). Average duration of affliction with migraine was 14.8 ± 8.5 years. Six patients reported having pronounced parasympathetic symptoms, such as tear production and nasal congestion/stuffiness during their attacks. The majority of patients had a family history of migraine, and in about 50% of the patients some attacks occurred during their menstrual period. There were no demographic and clinical differences between right-sided compared with left-side migraineurs. One left-sided migraine patient was eventually excluded from analysis because her forehead vascular responses were far larger than 2 SD above the mean. All migraineurs were studied during a headache-free interval (at least 1 week after their last attack). Patients were requested to report if they developed an attack during the successive 3 days after the experiment. However, none called. We also checked by randomly calling 20 patients, none of whom reported an attack.

**Procedures**

This single-session experiment was carried out in a quiet air-conditioned room in the laboratory, and conducted during the morning. The procedure used is fully described in our previous study (Avnon et al., 2003). In brief, two optic pulse sensors (photoplethysmography) were attached, one at each side of the forehead 1 cm above the eyebrows and 3 cm lateral to the midline, and a third sensor was attached to the palmar aspect of the right middle phalanx of the right middle finger. A continuous BP cuff (Finapres, Ohmeda, USA) was attached to the left middle finger, to evaluate heart rate and blood pressure values on a beat-to-beat basis.
After the subject had rested in a supine position for a few minutes, we recorded 10 min of baseline PPG signals and cardiovascular parameters. Then, we activated the parasympathetic system by instillation of one drop of diluted soap (Drummond, 1992, 1993; Avnon et al., 2003) into the conjunctival sac of one eye at a time. The soapy eyedrop was washed away with saline solution after 2 min. As a control, a drop of sterile saline was also administered to the eye, in single-blinded fashion, in a random sequence. After 15–30 min the other eye was similarly stimulated. This procedure was performed twice, in order to assess adaptation of the response. Patients were asked to estimate pain intensity for each drop, numerically, on a scale of 0 (no pain) to 10 (the most unbearable pain), following its administration.

**Photoplethysmography (PPG)**

PPG is a method that detects changes in arterial blood volume induced by cardiac activity by measuring the oscillatory changes in light reflection through the tissue. The PPG probes, described elsewhere (Nitzan et al., 1998; Babchenko et al., 2001; Avnon et al., 2003), consist of an infrared light source (LED) at 865 nm wavelength (Fujitsu, Japan) and a photodetector (Hamamatsu, S1223-01). The probes were attached to the skin of the forehead and finger as previously described. The maximum value of the PPG signal (attained at end of diastole) represents the baseline (BL). The PPG amplitude (AM) is the difference between the PPG values at its maximum (end-diastole) and at minimum (during systole), and is indicative of arterial compliance. We used an index consisting of the ratio of the two parameters, AM/BL, providing a parameter that is related to the amplitude of the tissue blood volume changes (Nitzan et al., 1998).

Changes in the trigemino-parasympathetic or sympathetic activation were evaluated by the measurement (in the forehead or finger, respectively) of the percentage change in AM/BL; the value of AM/BL during manipulation (AM/BL<sub>m</sub>) minus the value of AM/BL before manipulation (baseline) (AM/BL<sub>b</sub>) divided by the value of AM/BL before manipulation, expressed as a percentage: change (%) in AM/BL = 100 × (AM/BL<sub>m</sub> − AM/BL<sub>b</sub>) / AM/BL<sub>b</sub>.

The vascular and cardiovascular responses to ocular irritation were evaluated at three time points: the peak of the response (the maximum change), which occurred immediately after drop instillation, and 1 and 2 min afterwards. The 1 and 2 min points provided a measure for the duration and extent of the response.

**Statistical analysis**

The study was designed to produce data regarding multiple parasympathetic parameters, under baseline and during activation in migraineurs and controls. Each parameter (except pain rating) was expressed as a percentage change from baseline (premanipulation period value). Subject classification (type of migraine or control) served as the independent variable.

Initial inspection of the various parameters determined the normality of the data distributions, which is important for subsequent parametric statistical analyses.

We performed a preliminary series of individual, repeated measures (or mixed model) analyses of variance (ANOVAs), with associated post hoc Tukey–Kramer HSD (honestly significant difference) tests, to assess parasympathetic changes between subject classifications.

Regression and correlation analyses were also employed to examine the relationship between various combinations of parasympathetic parameters, pain ratings, cardiovascular parameters, and other responses.

Results are given as least square mean ± SE. P < 0.05 was considered statistically significant.

**Results**

### Forehead vascular responses to ocular irritation

**Overall response differences between left- and right-side migraineurs**

Preliminary analyses did not indicate significant differences between the first and second stimuli to right and left eyes, or between eyes. Therefore, these four readings were combined in the analyses.

Left-side migraineurs had significantly higher responses compared with right-side migraineurs; Peak ipsilateral (to stimulation) forehead vascular response (percentage change in AM/BL) obtained from stimulation of each of the eyes (an average of four readings) of left-side migraineurs was +60.1 ± 6.4% compared with +41.9 ± 6.4% (P = 0.05) in right-side migraineurs. Similar patterns were observed at 1 min (+32.9 ± 5.0% versus +15.6 ± 5.5%, P = 0.02) and 2 min after soap instillation (+20.3 ± 3.1% versus +7.3 ± 3.2%, P = 0.007) (Fig. 1A). Higher vascular responses in left-side migraineurs were also noted on the contralateral side of the forehead, but reached significance only 1 min after stimulation (Fig. 1B).

### Subanalyses of the forehead response to soapy stimulation data

(i) The first application seemed to induce a higher response than the second application, but there were no statistically significant differences in the vascular response between first and second soap application to each eye. Therefore, we collapsed the data between the first and the second stimuli together (a combination of two readings).

(ii) The immediate response to stimulation of the left eye in left-side migraineurs was higher than the immediate response to stimulation of the right eye in right-side migraineurs (+69.7 ± 6.2% versus +42.8 ± 6.1%, P = 0.05). Subsequent readings did not reach significance at 1 (+40.4 ± 6.0% versus +18.5 ± 5.9%, NS) or 2 min (+23.9 ± 3.8% versus +10.9 ± 3.8%, NS) after soapy drop administration (Table 1, Fig. 2).

Within the left-side migraineurs group, there was no statistically different ipsilateral forehead response between sides, regardless of stimulation side. The same pattern was seen for right migraineurs (Table 1).

### Vascular responses to saline eye drop

Saline eye drops produced vascular changes that were similar though milder and of shorter duration compared with the soapy eye drop. No differences were found between groups or between sides.
Pain ratings to ocular irritation

Pain rating to soapy eye drop in the left-sided migraine group was 6.2 ± 0.5 (range 3–10) and did not differ from that in the right-sided migraine group, with a rating of 5.3 ± 0.5 (range 2–10) \((P = 0.57)\). Group (left-sided and right-sided migraine) and individual ratings were similar for the right and the left eye and for the first and second soapy eye drops to each eye. Pain rating to soapy eye drop did not differ between sides, neither between symptomatic and non-symptomatic sides, in each migraine group.

Instillation of a saline drop in either eye produced no pain or mild pain sensation, which was not different between left-side \((0.8 ± 0.2)\) and right-side migraine patients \((0.3 ± 0.2)\) (least-squares mean ± SE).

Vascular response to ocular irritation measured from the finger

Digital blood volume decreased immediately after soapy drop instillation, as pulse amplitude (AM) decreased and the value of BL increased, resulting in a decrease in the parameter AM/BL, with early return to prestimulus values. There were no differences between sides in initial and successive instillations. There were no differences (average of all responses) between right-side \((-17.7 ± 4.1\%)\) and left-side migraineurs \((-15.9 ± 4.2\%)\) (Fig. 3).

Saline eye drops produced a slight and short-lasting decrease in the parameter AM/BL (vasoconstriction) in the finger, which was similar in magnitude between groups, and between sides in each group.

Heart rate responses to ocular irritation

Heart rate decreased slightly in response to the soapy eye drop (i.e. increase in heart period) in the two migraine groups. The increase in heart period was significantly higher in the left-side
migraine group compared with the right-side migraine group at the immediate response time (+6.2 ± 1.1% versus +3.1 ± 1.1%, \(P = 0.04\)) and at 1 min (+4.4 ± 0.8% versus +2.1 ± 0.8%, \(P = 0.05\)), and with a trend towards significance at 2 min (+2.7 ± 1.0% versus +0.04 ± 0.96%, \(P = 0.06\)) (Fig. 4). The heart period changes were significantly correlated (\(r = 0.57, P = 0.002\)) with the forehead vascular changes in response to soapy eye drops.

Discussion

Our results demonstrate differences in cutaneous and cardiac parasympathetic responses between strictly right and left side symptomatic migraine patients; left-side migraineurs had higher forehead vasodilatation and more pronounced bradycardia in response to ocular irritation compared with right-side migraineurs, indicating higher somato-parasympathetic responsiveness. Right-side migraineurs, however, did not express an increase in the somato-sympathetic reflex, as measured by finger vasoconstriction.

The somato-autonomic reflexes

The trigemino-parasympathetic reflex is characterized by facial vasodilatory and secretory responses, mediated by parasympathetic innervation, evoked by a painful stimulation to the tongue, lips, tooth pulp, nasal mucosa or eyes (Drummond, 1992, 1993, 1995; Drummond and Lance, 1992; Kemppainen et al., 1994; Shoji, 1996; Izumi, 1999; Izumi et al., 2002; Avnon et al., 2003). In this study, we instilled a diluted soapy eye drop and recorded the vasodilator response of the facial skin. The effenter part of the reflex is mediated by parasympathetic fibres employing primarily vasoactive intestinal peptide (Goadsby and Macdonald, 1985; Goadsby and Edvinsson, 1994) and possibly also nitric oxide (Nozaki et al., 1993) as neurotransmitters. These efferent parasympathetic fibres originate from the superior salivatory nucleus in the brainstem (Spencer et al., 1990), travel with the facial nerve and synapse at the sphenopalatine ganglion (Suzuki et al., 1988), often also called the pterygopalatine ganglion (Warwick and Williams, 1973). Thereafter they distribute to the end organs via several rami. Animal studies have documented this reflex activity and its pathways: electrical stimulation of the ophthalmic division of the trigeminal nerve (Gonzalez et al., 1975; Lambert et al., 1984), the trigeminal ganglion (Lambert et al., 1984; Goadsby et al., 1988; Goadsby and Edvinsson, 1993, 1994) or the greater superficial petrosal nerve (Lambert et al., 1984) increased release of jugular vein vasoactive peptides, facial flushing and forehead temperature and reduced carotid resistance. A similar finding of augmented bilateral forehead vasodilatation in response to a unilateral painful cutaneous or mucosal stimulation in the ophthalmic territory was documented in ictal and inter-ictal cluster and migraine patients (Drummond and Lance, 1992; Drummond, 1995, 1997). The bilaterality is in line with the anatomy of the parasympathetic innervation, since these fibres cross over in the brainstem (Lambert et al., 1984), and since in the rat at least each of the sphenopalatine ganglia innervate vessels on the ipsilateral and (to a lesser extent) the contralateral cerebral side (Suzuki and Hardebo, 1991).

The somato-parasympathetic reflex has been suggested to be involved in some of the vascular changes during headache, and to mediate the flushing, lacrimation and rhinorrhoea commonly observed during cluster headache and some migraine attacks (Drummond, 1992, 1995, 1997; Goadsby and Edvinsson, 1994).

Apart from differences in parasympathetic activity, the differences found between right and left migraineurs in forehead vascular responses could potentially result from differences in: (i) pain perception and processing, (ii) sensory C-fibre-based axon reflex responses; and (iii) sympathetic vasodilator responses. Our left- and right-side migraineurs reported similar pain rating in response to the soapy eye drops for both sides. This is in keeping with many reports that found no difference between the two sides in stimulus-evoked pain in pain-free migraineurs (Drummond, 1987; Jensen et al., 1988; Schoenen et al., 1989; Marlowe, 1992; Bovim, 1992; Drummond, 1997; Drummond and Lance, 1992; Kemppainen et al., 1994; Shoji, 1996; Izumi, 1999; Izumi et al., 2002; Avnon et al., 2003).
Vanagaite et al., 1997; Vingen et al., 1998; Becser et al., 1998; Katsarava et al., 2002; Sandrini et al., 2002; Milanov and Bogdanova, 2003). Our finding of similar pain ratings in response to ocular irritation for right and left migraineurs excludes the afferent factor from any explanation of our results.

Regarding axon reflex mechanism, Lambert and colleagues reported that only a small proportion of the vascular response to trigeminal stimulation is due to antidromic release of vasoactive substances from pain sensors in a cat model (Lambert et al., 1984). Furthermore, absence of forehead vascular response to ocular irritation on the injury side in patients with facial nerve palsy, where parasympathetic fibres are compromised while sensory fibres are spared, rules out the antidromic mechanism as a mediator of this vasodilatation (Drummond, 1992). Moreover, an afferently mediated axon reflex vasodilatation should be limited to the territory of stimulation and not cross to remote areas, such as the contralateral side, whereas our previous (Avnon et al., 2003) and present results show significant contralateral forehead vasodilatation in response to ocular irritation. In line with this, Satoh-Kuriwada and colleagues also observed a significant contralateral vasodilatation in the maxillary gingiva in response to electrical tooth stimulation in humans (Satoh-Kuriwada et al., 2003). They also excluded an axon reflex-mediated mechanism and proposed that the gingival vascular response is a centrally mediated parasympathetic reflex.

Sympathetic vasodilator involvement in the facial vascular response can also be ruled out. In sympathectomized animal models, electrical stimulation of the trigeminal nerve evokes a reflex vasodilatation in the lower lip, submandibular gland and palatal mucosa, which is necessarily non-sympathetic (Izumi and Karita, 1992, 1994; Date et al., 2000). In human studies, stellate ganglion blockade had no effect on the forehead vascular response to ocular irritation, which was similar on the blocked and intact sides (Drummond, 1993). Similarly, surgical sympathectomy in humans did not alter the maxillary gingival blood flow increase in response to electrical stimulation of the mandibular tooth pulp (Satoh-Kuriwada et al., 2003). These two human studies demonstrate that sympathetic efferents do not participate in the centrally mediated reflex vasodilatation following painful facial/orofacial stimulation. Our findings are also in line with this concept, as similar sympathetically derived finger vasocostriction was shown for right- and left-side migraineurs, in contrast to different facial vasodilatation.

For the vasococontractor somato-sympathetic reflex, a somatic stimulus, usually painful, is used to evoke a vasoconstrictive sympathetic response. In the present study we used the soapy eye drop as the painful stimulus to evoke both reflexes, and a finger PPG signal as a reflection of the resulting vasocostriction of the sympathetic response. Our patients had an average decrease of 17 ± 4.2% in finger pulse amplitude in response to soapy drop irritation. A decrease of similar order of magnitude has been reported due to painful stimulation at various sites (Cohen et al., 1978; Feuerstein et al., 1982; Kroner-Herwig et al., 1988; Kemppainen et al., 1994; Avnon et al., 2003).

In a previous study (Avnon et al., 2003) our group has shown that unilateral migraineurs, pooled together regardless of migraine side, had a smaller vasodilatory response of the facial skin compared with controls and with migraineurs with alternating and bilateral head pain. We suggested an augmented inhibitory interaction between the two loci of coerulei in the brainstem as a possible explanation to that finding. Patients in the present study, some of whom also served in our previous study, demonstrated the same pattern, as both the right- and the left-sided groups had less vasodilatation than controls. It seems, though, that the reciprocal inhibition is not symmetrical, as left-sided migraineurs expressed a higher degree of vasodilatation compared with the right-sided migraineurs. This could stem from augmentation of the parasympathetic tone at various levels of the left side of the CNS at the insula, hypothalamus and/or the brainstem.

Suprabulbar control of the parasympathetic reflex

The anatomy of the somato-parasympathetic reflex has been described at the brainstem level, and has so far been considered symmetrical. Our data show, for the first time, asymmetry of this reflex, which cannot be explained by known brainstem physiology and is, therefore, most likely under the control of higher centres, possibly the hypothalamus. The hypothalamus contains neuronal groups that project to autonomic centres of the brainstem and spinal cord (Swanson, 1987, 1991), and among its many autonomic functions it is involved in modulation of autonomic reflexes such as the baroreceptor (Spyer, 1990) and light (Hey et al., 1985) reflexes. Indirect data suggest that it might also be involved in the somato-parasympathetic reflexes in animals; Matsuo and Kusano (1984) reported that the lateral hypothalamus is involved in modulation of the parasympathetic gustatory–salivary reflex by demonstrating that electrical stimulation of the lateral hypothalamus increased neural activity of preganglionic parasympathetic fibres as well as salivary secretion, in response to stimulation of the tongue with high concentration of chemical solutions (NaCl, HCl), and in response to pinching the tongue in rats. Chyi and colleagues investigated transmitter mechanisms involved in vasodilatation in extracranial vascular beds due to dorsal facial area activation (Chyi et al., 1995). Among their findings, they reported that in decerebrated cats greater vasodilatation was produced by activation of the dorsal facial area compared with the vasodilatation produced in intact cats. They reported that the vasodilatation was mediated through parasympathetic mechanisms, and suggested that intercollicular decerebration might eliminate an inhibitory influence from higher structures to the dorsal facial area (Chyi et al., 1995). This idea was supported by the observations of Izumi and Karita (1997), who studied the effects of electrical

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stimulation of the anterior hypothalamus on lip blood flow. Such stimulation elicited attenuation of the lip blood flow increase reflexly evoked by lingual nerve stimulation. Izumi and Karita (1997) suggested that the anterior hypothalamus could inhibit parasympathetic reflex vasodilatation in the orofacial area region. Collectively, these data indicate the existence of a modulatory mechanism by which the hypothalamus can influence parasympathetic reflex vasodilatation in the cranial and extracranial vasculature.

Several human studies by May and colleagues also support hypothalamic involvement in the trigeminal reflex (May et al., 1998, 1999, 2000). PET studies (May et al., 1998, 2000) during nitroglycerin-evoked cluster attack, accompanied by ipsilateral autonomic facial symptoms, demonstrated unique activation of the ipsilateral hypothalamus, in addition to activation of various brain areas involved in pain processing. Similar ipsilateral hypothalamic activation, measured by functional MRI, was demonstrated in a patient during a spontaneous attack of short-lasting neuralgiform headache with conjunctival injection and tear production (May et al., 1999).

**Brady-cardia in response to facial stimulation**

Brady-cardia was evoked in normal subjects in response to instillation of diluted soap in the eye (Nordin and Fagius, 1995). Brady-cardia is also evoked in the diving reflex as a response to facial immersion in ice water (Gandevia et al., 1978; Finley et al., 1979). Similarly, the oculocardiac reflex elicited by pressure applied directly to the closed eyelid (Aschner, 1908), and the reflex elicited by nasopharyngeal stimulation (Gandevia et al., 1978) are known to slow the heart rate. The evoked brady-cardia in these reflexes is mediated mainly by the vagus nerve; the increased vagal activity in response to the diving reflex is abolished by section of the vagal nerve or by atropine administration and is not affected by sympathetic blockade by propranolol or phentolamine (Finley et al., 1979). The greater extent of brady-cardia in our left-side patients compared with the right-side patients could also be explained by predominance of the left side autonomic pathways.

**Autonomic differences between right and left-sided migraine patients**

Several studies are in line with our findings of different autonomic tone between right- and left-sided migraine patients. Gruzelier and colleagues measured interictal skin electrodermal responses in unilateral migraineurs, and found that left-sided pain was associated with under-responsiveness and fast habituation while right-sided pain was associated with over-responsiveness and slow habituation (Gruzelier et al., 1987). They suggested that the extent of sympathetic response was predictive of the laterality of pain in migraine.

A recent transcranial Doppler study by Chernyshev and colleagues also demonstrated autonomic differences between right- and left-side migraineurs during the headache-free period (Chernyshev et al., 2001). They measured blood flow velocity and pulsatility index (PI, maximum systolic flow velocity minus minimum diastolic flow velocity divided to mean flow velocity) and found that the PI of the middle cerebral artery on the headache side in right-side migraineurs was higher than the corresponding PI index in the left-side migraineurs. In addition, mean flow velocity of the basilar artery was higher in patients with right-sided headache than in the left-sided group.

The association between the laterality of pain and laterality in hemisphere function was elegantly highlighted by Fasmer and Oedegaard (2002). They studied migraine patients with comorbid unipolar depressive and bipolar disorders. They found that among the unipolar patients, in whom the right hemisphere seems to predominate in several cognitive functions, the migraine pain was predominantly located on the right side of the head. In turn, for bipolar patients, in whom the left hemisphere may be more active, the migraine pain was predominately located on the left side of the head. These results may suggest that the side of migraine pain is associated with the activity level of the corresponding hemisphere. In accordance with the findings of Fasmer and Oedegaard (2002), Crisp (1981) demonstrated that patients with left-sided migraine had low levels of anxiety and depression compared with other migraine patients. Activation of the left hemisphere is associated with positive emotions (Cummings, 1993; Davidson, 1995; Canli et al., 1998; Davidson and Irwin, 1999), and lesions of left frontal–subcortical circuits or of anterior temporal lobe regions often result in depression. Yet Brandt and colleagues failed to find personality or emotional differences attributable to headache laterality (Brandt et al., 1990).

Interestingly, a relation of autonomic imbalance with laterality of pain was found in cluster headache patients (Micielli et al., 1993). Micielli and colleagues evaluated the relation between 24 h HR changes during both cluster and remission periods, in relation to the side of pain. They found that pain on the right side resulted in a reduction in HR variability (day to night changes) when compared with the left-side patients, in both the cluster and the remission period. A trend to a high degree of arrhythmia was observed in the right-side cluster headache patients. In contrast to the above findings, they also noted that the daytime HR of right-side patients was significantly lower than that of the controls and the left-side patients. Micielli and colleagues concluded that cluster headache is associated with autonomic imbalance (Micielli et al., 1993). The results of Micielli and colleagues demonstrate autonomic differences between right- and left-side cluster headache patients, with probable greater sympathetic predominance for the right- compared with the left-side patients. Laterality of autonomic function in cluster headache may result from an influence of the ipsilateral hypothalamic (May et al., 1998, 2000).

In conclusion, this study demonstrates that left-side migraineurs have a predominant parasympathetic activation in response to pain compared with right-side migraineurs.
could stem from greater reactivity of left-sided autonomic centres. The side of the migraine, however, does not affect the extent of sympathetic activation. This might be related to the more generalized character of the sympa-thetic function (Low, 1997). Since both parasympathetic and sympathetic fibres innervate cerebral vessels and can influence brain metabolism and oxygenation, this lateralized differential effect might be of importance in the pathogenesis of migraine.

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