

Verisimilitude (or “truthlikeness”) as an alternative to pros and cons: migraine and cluster headache mechanisms

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Abstract Calculating verisimilitude (or “truthlikeness”) ad modum Popper is a quantitative alternative to the usual pros and cons in migraine and cluster headache mechanisms. The following items were evaluated: dilation of large cranial arteries during migraine; CGRP increase during migraine; migraine as a brain disorder; aura and migraine headache; brain stem activation during migraine; rCBF in migraine without aura; NO and pathophysiology of migraine; neurogenic inflammation and migraine; aura in cluster headache; and hypothalamic activation in cluster headache. It is concluded that verisimilitude calculations can be helpful when judging pathophysiological problems in migraine and cluster headache.

Keywords Migraine · Cluster headache · Pathophysiology · Mechanism · Verisimilitude

What Hume called our ‘natural instincts’ are stronger than any philosophical argument. In my view this applies to science as well.
Peter Lipton, 2005 [1].

Introduction

Pathophysiological studies of migraine often involve new techniques to reveal abnormalities compared with a control

group. Alternatively, an intervention provokes a migraine attack [2–5], with patients assessed before and after the intervention. Migraine research is increasingly hypothesis driven as migraine mechanisms become better understood [6, 7].

Philosopher of science Sir Karl Popper stated, “a good theory...makes a number of predictions that can in principle be disproved or falsified by observation” [8]. Established methods for comparing drug effects [9] include designing randomized clinical trials based on the null hypothesis. Additionally, systematic reviews or meta-analyses can estimate effects within 95% confidence intervals (CI) [10–13]. Systematic meta-analyses are not applicable to migraine mechanism theories and differing results with different methodologies prevent direct comparisons. To deal with such situations, Popper introduced the concept of verisimilitude (or “truthlikeness”) [14] to score the degree of likelihood of truth in a theory or statement. The concept has advantages over the *pros* and *cons* that are normally used where there are disagreements, as often occur in headache research. We applied the concept to several important migraine and cluster headache mechanisms. This exercise is aimed toward enlightening the migraine research field and to indicate where further research is needed.

Methods

Verisimilitude (or “truthlikeness”) of a theory a can be expressed ad modum Popper [14] as:

$$Vs(a) = CT_v(a) - CT_f(a)$$

where $Vs(a)$ is the verisimilitude of a , $CT_v(a)$ is a measure of the truth content of a , and $CT_f(a)$ is a measure of the falsity of a [14].

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When calculating $V_s(a)$ in Table 1, both $CT_v(a)$ and $CT_f(a)$ were given arbitrary values of 0, 0.25, 0.5, 0.75, or 1.0 for simplicity. The results for verisimilitude, $V_s(a)$, can thus be -1.0 (very unlikely), -0.75 (most unlikely), -0.5 (unlikely), -0.25 (probably unlikely), 0 (undecided), $+0.25$ (probably likely), $+0.5$ (likely), $+0.75$ (most likely), or $+1.0$ (very likely).

To exemplify, we chose both easy problems and problems requiring extensive comments and where the result of the analyses remains open for discussion. Our judgment of the evidence, indicated as $CT_v(a)$ and $CT_f(a)$, is given in Table 1 together with the calculated $V_s(a)$.

Results and comments

Does dilation of larger cranial arteries cause the pain in migraine headache?

Extracranial arterial vasodilation is traditionally regarded as the cause of migraine headache [15, 16]. Increased temporal pulsations were observed during migraine, and these pulsations decreased after intravenous ergotamine in parallel with the effect on headache [15]. Decreased blood velocity in the middle cerebral artery (MCA) during migraine, measured with transcranial Doppler (TCD), was found [17]. Since the cerebral blood flow was unchanged, it indicated dilation of the MCA [17]. This finding was confirmed with TCD in two small studies in 25 [18] and 10 [19] patients, respectively. The $CT_v(a)$ is 1.0.

In two relatively large studies with 31 [20] and 51 [21] patients, respectively, no decrease in blood flow velocity was found with TCD during migraine attacks. Furthermore, a recent magnetic resonance angiography (MRA) study found no MCA or extracranial part of the middle meningeal artery (MMA) dilatation during nitroglycerin-induced migraine ($n = 20$) [22]. Arguably, a negative study could theoretically be caused by variability in measurements, but in the MRA study [22], MMA (17%) and MCA (11%) vasodilation was observed during the 20-min infusion of nitroglycerin. We judge the $CT_f(a)$ to be 1.0. The verdict is still out concerning large cranial artery vasodilatation during migraine and the verisimilitude is 0.

Is calcitonin gene-related peptide (CGRP) increased in the external jugular vein (EJV) during migraine attacks?

For many years it has been known that CGRP is increased in the EJV blood during migraine attacks [23, 24] leading to the conclusion that CGRP is a neuropeptide elevated during migraine attacks [25]. In a study of very long-

standing attacks (median 11 h), sumatriptan treatment normalized CGRP levels [24]. The $CT_v(a)$ is 1.0.

Calcitonin gene-related peptide (CGRP) was unchanged in two spontaneous migraine studies [26, 27]. Both the studies used intra-patient design [26, 27]. In one study [26], two CGRP analyses methods were used including a method used previously by Goadsby et al. [23, 24], but no change in CGRP was observed. Furthermore, in one nitroglycerin-induced migraine attack study, CGRP was not increased [27]. The $CT_f(a)$ is 1.0. Currently, there is similar evidence for and against increased CGRP in the EJV, and the verisimilitude is 0.

Is migraine a dysfunction of the sensory modulatory network?

Most neurologists agree that migraine starts in the brain and confer the prodromes and aura, but their opinions about the headache phase differ. Recently, a proponent of pure CNS pathophysiology stated, “Migraine is a dysfunction of the sensory modulatory network with the dominant disturbance affecting abnormal processing of essentially normal neuronal traffic” [7].

The prodromes that occur in 30% of patients [28] and auras that occur in 20% of patients [29] must originate in the CNS. During aura, there is a characteristic spreading oligemia in the cerebral cortex [30–32]. Other evidence for CNS involvement during migraine attacks is available. Persistent brain stem activation was observed by PET during migraine attack [4, 33, 34]. Additionally, hypothalamic activation is observed during migraine attacks [34]. Few cases of symptomatic migraine caused by brain stem lesions are reported [35, 36]. Other migraine symptoms, such as photo- and phonophobia, are without peripheral cause [7]. β -blockers used as migraine prophylactics probably exert their effect in the CNS [37]. Valproate and topiramate also probably work in the CNS [29]. In rats, chronically administered prophylactic migraine drugs like propranolol, valproate, topiramate amitriptyline, and methysergide suppressed CSD frequency and increased the cathodal stimulation threshold required to evoke CSD [38]. Additionally, 5-HT_{1B/1D} receptors are present in the brain stem [39], which could explain the efficacy of triptans and alkaloids in migraine. There are many pros and the $CT_v(a)$ is 1.0.

In an animal model of migraine, c-fos expression and the “evoked potential” are observed in the trigeminal nucleus caudalis (TNC) after superior sagittal sinus stimulation in the cat [40–43]. There appears to be a peripheral source for this “brain stem” activity in the animal migraine model. CSD activates trigeminal afferents, resulting in a series of cortical, meningeal, and brain stem events consistent with the development of a process similar to

Table 1 Verisimilitude calculations for proposed migraine and cluster headache mechanisms (for details, see text)

Hypothesis (prediction)		
$V_s(a)$	$CT_v(a)$	$CT_f(a)$
Vasodilation of large cranial arteries is involved in migraine pain		
Vasodilation of large arteries during migraine is undecided (0)	Increased temporal pulsations during migraine and the effect of ergotamine [15]. Decreased blood velocity in MCA during migraine measured with TCD [17–19] (1.0)	No change in MCA velocity measured with TCD [20, 21] No vasodilatation measured directly with MCA in MMA and MCA during NTG-induced migraine [22] (1.0)
Calcitonin gene-related peptide (CGRP) is increased in the external jugular vein (EJV) during migraine		
CGRP increase in EJV during migraine remains undecided (0)	CGRP was increased in EJV in two studies [23, 24]. In one study, sumatriptan treatment normalized CGRP levels [24] (1.0)	CGRP was unchanged in two studies on spontaneous migraine [26, 27] and one study in nitroglycerin-induced migraine [27] (1.0)
Migraine is a dysfunction of the sensory modulatory network with the dominant disturbance affecting abnormal processing of essentially normal neuronal traffic [7]		
Whether a migraine attack is a pure neuronal process without vascular components being involved is unresolved (0). See text	A migraine attack must start in the brain to cause the prodromes and aura. Persistent activation in the brain stem is observed by PET during migraine attack [4, 33]. Few cases of symptomatic migraine are caused by brain stem lesions [35, 36]. Other migraine symptoms, photo- and phonophobia, have no peripheral cause [7]. The β -blockers used in migraine prophylaxis probably exert their effect in the CNS [37]. Valproate and topiramate also most likely work in the CNS [29] (1.0)	C-fos expression and “evoked potential” are observed in TNC after superior sagittal sinus stimulation in the cat model of migraine. [42]. There may be a peripheral source for activity. No other part of the body experiences pain without nociceptive input, except thalamic pain and other neuronal lesions with sensory sign [129]. A pure neuronal disorder does not explain the comorbidities of migraine with aura and stroke and ischemic heart disease [48, 49, 129]; a vascular or systemic factor must be involved. A central theory would not explain possible CGRP increases in EJV [23, 24]. Systemic endothelial dysfunction present in migraine [127] (1.0)
Does aura trigger headache in migraine attacks?		
Aura is likely to trigger a migraine attack (+0.25)	Clinically, the headache in migraine is contralateral to aura in 92% [58] Experimentally, CSD activates trigeminal afferents and evokes a series of cortical meningeal and brain stem events consistent with headache development in rats [44]. CSD activates matrix metalloproteinase, which opens the blood–brain barrier [62] (0.75)	Clinically, there are well-documented cases of headache ipsilateral to aura [57]. Patients with aura but no headache challenge the notion that aura causes headache. [57]. Aura does not necessarily precede headache [57]. Experimentally, no correlation between CSD and neurogenic inflammation and nociception in rats. [66] (0.5)
Brain stem activation occurs during spontaneous and provoked migraine attacks		
Brain stem most likely activated during migraine, but lateralization doubtful; pathophysiological implications somewhat unclear. (+0.75)	Two PET studies in spontaneous [33, 34] and one in NTG-induced migraine [4], showed brain stem activation which persisted after sumatriptan treatment [4, 33, 34] (1.0)	Lateralization of activation and pain is inconsistent. In one study, PET activation was ipsilateral [4], in two others contralateral [33, 34] or bilateral [34] to pain (0.25)
Regional cerebral blood flow (rCBF) is normal in migraine without aura		
No firm conclusions (0)	rCBF measurements were normal in one SPECT study [68]. Brain stem activated in migraine but no occipital hypoperfusion observed by PET [4, 34]. Normal rCBF measured with PWI [69] (1.0)	Occipital hypoperfusion was observed with PET ($n = 6$) [73]. Spreading oligemia observed with PET in one case [74]. A SPECT study showed focal hypoperfusion in 74% of patients [70]. Patchy hypoperfusion was observed [71]. Small general reduction of CBF [72] (1.0)
NO is involved in migraine pathophysiology. iNOS inhibitors will be effective migraine prophylactics		
NO is likely involved in migraine (+0.5)	Nitroglycerin induces genuine migraine attacks [22, 75–83]. L-NMMA is effective in migraine [84] (1.0)	iNOS inhibitors (GW273629, GW274150) were ineffective in treating migraine attacks [85, 86]. GW274150 was ineffective as a prophylactic agent [86, 87] (0.25)

Table 1 continued

Hypothesis (prediction)		
Vs(<i>a</i>)	CT _v (<i>a</i>)	CT _f (<i>a</i>)
Dural neurogenic inflammation (NI) is involved in migraine, predicting effectiveness of NI inhibitors in migraine		
NI unlikely to have a pivotal role in migraine pain (−0.5)	Endothelin and NK-1 receptor antagonists effectively inhibit NI in animal studies [94, 95]. In addition, triptans and ergot alkaloids inhibits NI [90, 91] (0.5)	Randomized clinical trials show no effect of substance P, neurokinin-1 antagonists [96–98], neurosteroid ganaxolone [99], endothelin antagonist [100], or specific NI blockers [101, 102] (1.0)
Aura is common in cluster headache patients [Schürks-et al-2006] ^a		
Aura must be rare in cluster headache (−0.5)	Aura occurred in 4% [106], 14% [103], 23% [104], and 28% [105] of cluster headache patients (0.5)	None of 554 cluster headache patients experienced aura [111] (1.0)
Hypothalamic activation is specific for cluster headache and other trigeminal autonomic cephalalgia (TAC) [133]		
Hypothalamic activation is not cluster headache specific; the Popper falsification rule [8] was used	Activation in the posterior hypothalamus during nitroglycerin-induced cluster headache attacks was observed by PET [112, 113]. In migraine without aura, no hypothalamic activation was found in two PET studies [4, 33]. In two SUNCT patients, functional MRI identified hypothalamic activation [116, 117]	Activation was observed in both the hypothalamus and brain stem (<i>n</i> = 7) with PET [34]

headache pain transmitted by the trigeminal nerve in this animal model of migraine with aura [44]. In another study, CSD directly activated trigeminovascular nociceptors without perivascular meningeal inflammation (the dura mater was not examined) [45].

If the carotid artery is occluded ipsilateral to the side of migraine headache then two-thirds will experience relief [46] indicating that cranial arteries are involved in migraine pain. The co-morbidities of migraine with aura and stroke, ischemic heart disease, and cervical arterial dissection [47–53] indicate a vascular or systemic component in migraine. The possible increased release of CGRP [23, 24, 54] in the external jugular vein is probably due to CGRP released locally from perivascular nerves. The small possible “infarcts” observed with MRI in the posterior cerebral circulation [55] indicate a vascular genesis. Brachial artery diameter (mean 4.82 vs. 5.39 mm) and compliance (mean 0.30 vs. 0.37 mm²/kPa) were decreased in migraine patients compared with controls [56]. Carotid arterial wall properties were similar between groups [56]. The CT_f(*a*) was 1.0 and the verisimilitude was 0.

Does aura trigger the headache in migraine attacks?

The relationship between aura and headache in migraine with aura has been questioned [57]. Some clinical evidence for a relationship exists. Thus, 35 (92%, 95 CI: 79–98%) out of 38 patients in whom both aura and headache were unilateral, felt that the headache and the aura were contralateral to each other; i.e. the headache was perceived

over the affected hemisphere [58]. Aura and headache were perceived as ipsilateral only in 3 patients. Notably, the results were obtained with prospective-symptom recording. As much as 19 patients had bilateral headache and could not provide evidence on whether or not aura triggers headache [58].

Experimentally, CSD activates trigeminal afferents and evokes a series of cortical meningeal and brain stem events [44]. Several other animal studies showed that CSD can cause activation of the brain stem [59–61]. CSD activates matrix metalloproteinases, which open the blood–brain barrier [62]. In one study, activation of trigeminovascular nociceptors by CSD occurred without perivascular inflammation [45]. Neurogenic inflammation is, however, unlikely to be involved in migraine pain or in the link between aura and headache. Overall the CT_v(*a*) is 1.0.

A clinical argument against aura as a migraine trigger is that most migraineurs never experience aura [29, 63], but the headache phase is, in principle, the same in migraine with or without aura [29]. Additionally, there are well-documented cases of headache ipsilateral to aura [57]. Patients with aura, but no headache are not uncommon [64, 65], challenging [57, 63] the notion that aura causes headache. Aura does not necessarily precede headache [57].

Experimental evidence against aura as a trigger of migraine pain comes from two studies in which there was no activation or sensitization of second-order neurons in TNC by CSD [66, 67]. The CT_f(*a*) is 0.5.

I believe aura is likely to trigger a migraine attack, and the verisimilitude is +0.5.

Is brain stem activation measured with PET present during migraine attacks?

In three PET studies, brain stem activation was observed [4, 33, 34]. This activation persisted after treatment with sumatriptan [4, 33, 34]. Therefore, in all PET studies conducted so far, brain stem activation was found and the $CT_v(a)$ is 1.0. However, there is an unexplained inconsistency concerning the lateralization of activation and pain. In one study, PET activation was ipsilateral to pain [4], whereas it was contralateral [33, 34] or bilateral [34] to pain in others. The $CT_f(a)$ is 0.25. Brain stem activation during migraine is probable. However, lateralization is doubtful, making the pathophysiological implications unclear and the final verisimilitude is +0.75.

Is regional cerebral blood flow (rCBF) normal during attacks of migraine without aura?

rCBF, measured with SPECT, was normal before and during 8 wine-induced migraines without aura attacks [68]. In two PET studies in migraine without aura attacks in either spontaneous ($n = 9$) [33] or GTN-induced ($n = 24$) [4] attacks, there was no occipital hypoperfusion. During spontaneous migraine attacks with a duration of 1–11 h, perfusion-weighted imaging reveals normal hemodynamic ($n = 13$) [69]. The $CT_v(a)$ is judged to be 1.0.

rCBF during spontaneous/induced migraine without aura attacks were investigated with SPECT ($n = 35$) [70] and 74% of patients displayed an unilateral hypoperfusion, mainly in the occipital region. In one PET study, there was generally no change in rCBF, but analysis of individual data showed patchy hypoperfusion in the temporo/occipital region in 4 patients with migraine without aura [71]. Global CBF was slightly, but significantly reduced in migraine without aura attacks compared with outside attacks ($n = 9$), 53 versus 60 ml/min/100 g, respectively [72]. Occipital hypoperfusion was observed in another PET investigation in established attacks without aura ($n = 6$) [73]. Spreading oligemia was observed with PET in one case [74]. The resulting $CT_f(a)$ is most likely 1.0. Thus, no firm conclusion concerning rCBF in migraine without aura can presently be drawn and the verisimilitude is 0.

Is NO involved in migraine pathophysiology?

Glyceryl trinitrate induced migraine without aura with a latency of some hours in migraine sufferers, with and without aura, in 11 studies [2, 22, 75–83]. A double-blind, placebo-controlled design was used in two investigations [22, 78]. The NOS inhibitor, L-NMMA effectively treated migraine attacks [84]. The $CT_v(a)$ is 1.0.

However, the two iNOS inhibitors GW274150 and GW273629 were ineffective in treating migraine attacks in one placebo-controlled study ($n = 126$) [85] and in an open-label pharmacokinetic study [86]. Additionally, GW274150 was ineffective in a double-blind, placebo-controlled study as a prophylactic agent for migraine ($n = 430$) [87]. Since other NOS isoforms (nNOS and eNOS) may be involved in the effect of NO [88], the $CT_f(a)$ is 0.25.

NO is most likely involved in the pathophysiology of migraine with a verisimilitude of +0.75.

Is neurogenic inflammation (NI) involved in the headache aspect of migraine?

If dural NI is involved in migraine, as proposed by Markowitz et al. [89], NI inhibitors would be predicted to be effective in migraine. This is true to some extent because ergot alkaloids and triptan inhibit NI [90, 91]. These drugs are, however, not specific NI inhibitors [92, 93]; however, endothelin and NK-1 receptor antagonists effectively inhibit NI in animal studies [94, 95]. The $CT_v(a)$ is 0.5.

Alternatively, several randomized clinical trials show no effect of substance P, neurokinin-1 antagonists [96–98], neurosteroid ganaxolone [99], endothelin antagonists [100], or the specific NI blockers CP122,288 and 4991w93 [101, 102] in the acute treatment of migraine. The $CT_f(a)$ is 1.0.

Since specific NI inhibitors have no effect in migraine, it is difficult to find a pivotal role for dural NI in migraine [7, 63] and the verisimilitude is –0.5.

Is aura common in cluster headache attacks?

The next subject is theoretically important. If aura is not only linked to migraine with aura, but also with other primary headaches, such as cluster headaches, aura and migraine could be caused by two different mechanisms [57, 103]. In a recent paper [104], aura was described as being common in cluster headaches, with 23% of cluster headache patients in the study experiencing aura. Similarly, aura was reported in 28% of cluster headache patients in a series of 76 patients [105]. In two earlier studies, aura was reported in 4 [106] and 13% [103], respectively, of cluster headache patients. In 1972, Graham mentioned that brief episodes of scintillating rarely, but occasionally occur before cluster headache attacks [107]. The $CT_v(a)$ for aura being common in cluster headache is thus 0.5.

Dr. Karl Ekblom from Stockholm, Sweden, an expert in cluster headache [108, 109] and migraine with aura [110], was asked his opinion. In a series of 554 cluster headache

patients, there were no cases of aura in connection with cluster headache attacks [111]. The $CT_f(a)$ is 1.0.

Aura is, therefore, likely to be rare in cluster headache patients, and the verisimilitude is -0.5 .

Hypothalamic activation is specific for cluster headache and other trigeminal autonomic cephalalgias

Functional PET imaging shed light on the genesis of migraine and cluster headache by repeatedly documenting activation in the midbrain and pons during migraine, and in the hypothalamus during cluster headache. Two PET investigations found activation in the posterior hypothalamus during nitroglycerin-induced cluster headache attacks [112, 113]. Voxel-based morphometry with MRI found changes in the same region [114]. Furthermore, with $^1\text{H-MR}$ spectroscopy, hypothalamic-*N*-acetyl aspartate/creatinine was reduced in patients with cluster headache versus controls [115]. In two patients with SUNCT, hypothalamic activation was observed with functional MRI [116, 117]. In paroxysmal hemicrania, hypothalamic activation was found with PET [118]. In hemicrania continua, with a phenotype in between cluster headache and migraine, activation was observed both in the hypothalamus and in the brain stem [119].

In migraine without aura, hypothalamic activation was not found in two PET studies ($n = 33$) [4, 33]. Hypothalamic activation concurrent with brain stem activation was observed in one PET study in migraine without aura attacks ($n = 7$) [34, 73]. These activations persisted after successful treatment with sumatriptan [34, 73].

In this case, the Popper falsification rule [8] seems appropriate. Hypothalamic activation is not specific to cluster headache because it was observed in migraine without aura in a study with appropriate PET techniques [34].

Discussion

Current migraine-mechanism theories vary from the notion that the migraine attack “consists of an abnormal perception of otherwise normal circumstances, such as pain without evidence of primary nociceptive activation” [7] to “migraine may be a local manifestation of a systematic vascular abnormality rather than a primary cerebral phenomenon” [120] or to “migraine is a neurovascular disorder” [121].

Popper’s verisimilitude calculation does not resolve problems always. Potentially, both the $CT_v(a)$ and $CT_f(a)$ can be 1.0 with a resulting verisimilitude of 0. Sometimes, one must fall back to the Popper falsification method, where negative facts that can falsify the hypothesis are the

main stay. Migraine data are often not validated well enough to allow clear-cut conclusions. Particularly, confirmatory studies using the same methodology are often lacking.

In areas like migraine research, which is often descriptive, many cases of contradictory data exist because of both biological variability per se and different methods of measuring the biological signal.

No grand unifying theory exists in migraine research that can be falsified by itself or by its predictions [8], leaving only isolated relevant problems of basic and clinical migraine research for testing.

When evaluating the problems, we often used a mixture of facts from both kinds of research. Verisimilitude determinations can supplement the usual pros and cons by forcing judgement of the evidence for hypothesis *a* when assigning values to $CT_v(a)$ and $CT_f(a)$ [14]. According to Popper, $V_s(a)$ calculation is an objective method for judging a scientific theory or the predictions derived from a theory [14].

Verisimilitude measures the best correspondence with facts and should not be confused with probability [14]. One can apply the simple verisimilitude formula to any field one knows well. Notably, verisimilitude calculations should not be applied to quantitative migraine treatment trials when a systematic review or meta-analysis is more appropriate [10–13].

Despite efforts at objectivity, some subjectivity remains in assigning values to $C_t(a)$ and $C_f(a)$. Some may disagree with my calculations, but anyone can easily assign alternative $C_t(a)$ and $C_f(a)$ values and calculate verisimilitude for themselves.

Among the 10 cases judged by verisimilitude calculations, there were two -0.5 (unlikely), four 0 (undecided), one $+0.25$ (probably likely), one $+0.5$ (likely), and one $+0.75$ (most likely) (Table 1). For one item, the falsification ad modum Popper [8] was found to be more suitable. There was no -1.0 (very unlikely), probably because there is always some historical or recent evidence for the hypothesis tested [89–91, 104, 105]. The -0.5 depend on the formulation of the question. In four cases, we could not decide whether the theory was true or false because the evidence for and against it was of equal weight.

The verisimilitude approach is not problem-free. To illustrate, I discuss two problems in detail: migraine as a pure CNS disorder, possible aura in cluster headache, and cortical spreading depression (CSD).

The theory that *migraine is a dysfunction of the sensory modulatory network* [7] can be re-formulated as *migraine is a pure human brain disease*. Many good arguments exist for both sides and the $CT_v(a)$ and $CT_f(a)$ will still be 1.0 with the facts used in my analysis (Table 1), and verisimilitude will be 0. However, when using my prerogative as

author and using our “natural instincts” (see vignette) combined with Popper’s falsification theory [8], I believe that the verisimilitude should be negative.

Thus, the theory that migraine is a brain disease would predict that there is no non-brain disorder associated with it. The main falsifying argument of this prediction is the cardiovascular comorbidity associated with migraine [56]. For example, there is an association between cervical arterial dissection and migraine, mainly migraine with aura [52, 53]. Additionally, migraine, particularly migraine with aura, is a risk factor for ischemic stroke [47, 56]. The arteries of the systemic circulation were also investigated [56, 120, 122]. Migraineurs with recent onset (<6 years) had decreased brachial arterial diameters and compliances [56]. Decreased flow-mediated dilatation of the brachial artery was also found in two other studies in migraineurs [120, 122].

Furthermore, some genetic arteriopathies are associated with migraine [123, 124] and in CADASIL, where the *notch-3* gene appears to be expressed exclusively in vascular smooth muscles within adult brain [125]. rCBF changes during migraine were similar in one case to migraine with aura [6, 126].

Circulating endothelial progenitor cell numbers and functions (i.e. endothelial repair markers) [127], are reduced, especially in migraine with aura patients [128]. In two studies [48, 129], the von Willebrand factor, a plasma marker of endothelial dysfunction, was increased in migraine. Thus, there is good evidence that migraine is associated with endothelial dysfunction, and could be the underlying link between migraine and cardiovascular risk [49, 128].

I believe that the arguments against the predictions of the neuronal theory of migraine falsify this theory [7]. Migraine is unlikely to be a brain-only disease. Another argument against the neuronal theory is that no other part of the human body experiences pain without nociceptive input except thalamic pain and other neuronal lesions with sensory signs [130]. In migraine, there can be allodynia, but no sensory signs [130]. I believe that, in addition to a clear CNS component, there is also a peripheral component in the headache phase. Regarding the source of pain, Goadsby recently stated “The pain process is likely to be a combination of direct factors, i.e. activation of the nociceptors of pain-producing intracranial structures, in concert with a reduction in the normal functioning of the endogenous pain control pathways that normally gate that pain” [7]. I agree that there is both a peripheral and central aspect of migraine headache. Because of the pulsating pain in migraine, I believe vascular nociception most likely [131] even though the verisimilitude of large arterial vasodilation during migraine was zero.

The question of aura in cluster headache

Four recent papers report prevalences of 4 to 28% for aura in cluster headache [103–106]. One may wonder how such a frequent and characteristic phenomenon went unrecognized by Baylor Horton, who described histaminic cephalalgia in 1938 ($n = 181$) [131]. Horton later in 1956 reported seeing 1,176 patients (1,023 men and 153 women) with histaminic cephalalgia [133]. Aura is not mentioned by Kudrow whose book from 1980 included 495 patients [132]. However, the cluster headache expert John R. Graham wrote “Now to our surprise we were able to establish that in 20 cluster headache patients brief episodes of scintillating scotoma rarely, but occasionally, did precede the cluster headache attacks” [107]. However, there are inconsistencies in the prevalences reported. The highest reported prevalence is 28% ($n = 76$) [105] and the lowest is 4% ($n = 101$) [107], a difference of 24% (95% CI 13–34%, $P < 0.0001$, Fisher’s exact test). The difference between the 23 [104] and 4% [106] prevalence is 19% (95% CI 13–26%, $P < 0.0001$). Also, prevalence was significantly different between the two largest studies: 23 ($n = 246$) [104] versus 13% ($n = 230$) [103], a difference of 10% (95% CI 2–16%, $P = 0.01$). These differences demonstrate that the method of registering “so-called aura” must have varied considerably.

In contrast, no reports of aura in cluster headache were reported in a large series of 554 cluster headache patients from one Swedish center [111]. Karl Ekblom, who has a special interest in aura [110], personally interviewed 427 patients, and observed and questioned about 100 of them during spontaneous or provoked cluster headache attacks [111].

Confronted with these incomparable data, it is a matter of belief or trust. Both sets of contradictory data cannot be an approximation of the truth and I calculated the verisimilitude to be -0.5 . In my opinion, aura must be rare among cluster headache patients.

In conclusion, I believe verisimilitude calculations are suitable for many migraine and cluster headache mechanism problems. Contradictory data concerning a specific problem are common and a verisimilitude calculation enforces a qualitative judgement of the data. Sometimes, the resulting verisimilitude is zero, but both, $CT_v(a)$ and $CT_f(a)$, cannot be an approximation of the truth. In some cases, further investigation is needed or a clearer hypothesis should be formulated, and appropriate investigations aimed at falsifying the thesis [8] should be performed. Finally, positive evidence is never conclusive; but neither is negative evidence, nor would it be a good idea to pretend that it was [1].

Conflict of interest None.

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