Review

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
2024, Vol. 44(10) 1–28

DOI: 10.1177/03331024241287224
journals.sagepub.com/home/cep

Sage

Insights from triggers and prodromal symptoms on how migraine attacks start: The threshold hypothesis

Gabriele Sebastianelli[1], Arife Çimen Atalar[2], Ilaria Cetta[3,4,5], Fatemeh Farham[6], Mira Fitzek[7], Hulya Karatas-Kursun[8], Marharyta Kholodova[9], Kadri-Hebo Kukumägi[10], Danilo Antonio Montisano[11], Dilara Onan[12], Aleksandar Pantovic[13], Jeva Skarlet[14], Dmytro Sotnikov[15], Edoardo Caronna[16,17], Patricia Pozo-Rosich[16,17] and on behalf of International Headache Academy of the International Headache Society (IHS-iHEAD)

Abstract

Background: The prodrome or premonitory phase is the initial phase of a migraine attack, and it is considered as a symptomatic phase in which prodromal symptoms may occur. There is evidence that attacks start 24–48 hours before the headache phase. Individuals with migraine also report several potential triggers for their attacks, which may be mistaken for premonitory symptoms and hinder migraine research.

Methods: This review aims to summarize published studies that describe contributions to understanding the fine difference between prodromal/premonitory symptoms and triggers, give insights for research, and propose a way forward to study these phenomena. We finally aim to formulate a theory to unify migraine triggers and prodromal symptoms. For this purpose, a comprehensive narrative review of the published literature on clinical, neurophysiological and imaging evidence on migraine prodromal symptoms and triggers was conducted using the PubMed database.

Results: Brain activity and network connectivity changes occur during the prodromal phase. These changes give rise to prodromal/premonitory symptoms in some individuals, which may be falsely interpreted as triggers at the same time as representing the early manifestation of the beginning of the attack. By contrast, certain migraine triggers, such as stress,

[1]Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome Polo Pontino ICOT, Latina, Italy
[2]Neurology Department, Health Sciences University, Istanbul Physical Therapy and Rehabilitation Training and Research Hospital, Istanbul, Turkey
[3]Neuroimaging Research Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy
[4]Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy
[5]Vita-Salute San Raffaele University, Milan, Italy
[6]Department of Headache, Iranian Center of Neurological Research, Neuroscience Institute, Tehran University of Medicine Sciences, Tehran, Iran
[7]Department of Neurology, Charité–Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany
[8]Institute of Neurological Sciences and Psychiatry, Hacettepe University, Ankara, Turkiye
[9]Department of Neurology and Neurosurgery, Medical Center "Dobrobut-Clinic" LLC, Kyiv, Ukraine
[10]University of Tartu, Tartu University Hospital, Tartu, Estonia
[11]Headache Center, Neuroalgology Dpt – Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy
[12]Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Yozgat Bozok University, Yozgat, Türkiye
[13]Neurology Clinic, Military Medical Academy, University of Defence, Belgrade, Serbia
[14]Western Tallinn Central Hospital, Tallinn, Estonia
[15]Department Neurosurgery and Neurology, Sumy State University, Medical Center "Neuromed", Sumy, Ukraine
[16]Headache Unit, Neurology Department, Vall d'Hebron University Hospital, Barcelona, Spain
[17]Headache Research Group, Departament de Medicina, Vall d'Hebron Institute of Research, Universitat Autonoma de Barcelona, Barcelona, Spain

Corresponding author:
Patricia Pozo-Rosich, Headache Unit, Neurology Department, Vall d'Hebron University Hospital, Barcelona, Spain; Headache Research Group, Departament de Medicina, Vall d'Hebron Institute of Research, Universitat Autonoma de Barcelona, Barcelona 08035, Spain.
Email: patricia.pozo@vallhebron.cat

hormone changes or sleep deprivation, acting as a catalyst in reducing the migraine threshold, might facilitate these changes and increase the chances of a migraine attack. Migraine triggers and prodromal/premonitory symptoms can be confused and have an intertwined relationship with the hypothalamus as the central hub for integrating external and internal body signals.

Conclusions: Differentiating migraine triggers and prodromal symptoms is crucial for shedding light on migraine pathophysiology and improve migraine management.

Keywords

hypothalamus, preictal, premonitory, prodromal phase, prodrome, triggers

Date received: 7 May 2024; revised: 28 August 2024; accepted: 30 August 2024

Introduction

Migraine is a cyclical neurological disorder characterized by recurring attacks and multiple phases: interictal, premonitory or prodrome, headache, and postdrome (1,2). The prodrome is the beginning of the migraine attack, representing the transition from the interictal to the headache phase (3), and is considered a symptomatic phase (4). The starting of the prodrome could result from cyclical pathophysiological changes in different brain networks (5), but certain triggers can also precipitate these changes and facilitate the attack. Indeed, a significant portion of people with migraine report that their attacks could be triggered by several factors (6,7). It is plausible that migraine triggers and prodrome have an intertwined relationship (8). In most cases, prodrome may cause behaviours that can be misinterpreted as triggers, but, in a minority of cases, certain triggers may mimic prodrome at the same time as actually acting as true triggers. Understanding this relationship and revealing the underlying mechanisms of the prodromal phase can highlight potential migraine initiation and progression steps. Furthermore, shedding light on this topic might lead to the development of new drugs to treat migraine attacks in their earliest phase, when they have more chances to be effective (9). This review will illustrate, in detail, both migraine triggers and prodrome to further explore and shed light on how the migraine attack begins.

Search strategy and selection criteria

This is a narrative literature review. The reviewers were divided into three groups and worked independently, performing an extensive literature search from the PubMed database using the search term "migraine" or "migraine cycle" in combination with the terms "triggers", "prodrome", "premonitory", "premonitory symptoms", "prodromal symptoms", "preictal", "preictal" and "MRI", "preictal" and "neurophysiology", "prodrome" and "MRI", and "prodrome" and "imaging".

Additionally, papers from references cited in relevant articles were identified. No publication date restrictions were applied, but we preferentially selected original articles published in the last ten years. Reviews were selected when space did not allow a more comprehensive discussion. We excluded letters to editors, pediatric studies, and articles published in languages other than English.

Each group selected the relevant articles and resolved the conflicts with each other through serial discussions. Two of the reviewers (GS and EC) supervised the main working groups. After the initial round of discussions, all researchers evaluated the full texts of the relevant studies in detail regarding research quality and generated the exact study reference list. The senior reviewers (PPR and EC) solved the unresolved conflicts and approved the final reference list.

Definition of triggers and prodrome

Migraine prodrome

The prodrome, also known as the premonitory or prodromal/preictal phase, is considered the initial phase of the migraine attack and is defined as a symptomatic phase that occurs before the onset of headache in migraine without aura or before the aura in migraine with aura (4). Although this phase may extend up to 72 hours in some attacks, clinical, electrophysiological, and neuroimaging studies provided evidence that it lasts up to 48 hours in most cases (10–12).

Nonpainful symptoms, the so-called prodromal/premonitory symptoms (PSs), can occur during this phase. The most frequently reported PSs in clinical studies are fatigue, neck pain, mood changes, photophobia, yawning, dizziness, difficulties in concentration, appetite changes (craving), and nausea (Table 1). They can be broadly categorized into mood and cognitive changes, homeostatic and hormonal changes, and sensory sensitivities (3). Occurring days or hours before the headache phase, PSs may enable some individuals with migraine to foresee their migraine attacks (1,13,14). According to a study by Giffin et al. (12), patients who experienced PSs correctly predicted the following attack 75–95% of the time within the following 72 hours. Similar findings were observed by Gago-Veiga

Table 1. Range of frequency of prodromal symptoms in clinical studies (prodromal symptoms that were investigated by only one study were not reported).

Category	Prodromal symptom	Reference	Number of patients (n = sample size)	Range of frequency (mean)	Prodromal symptom	Reference	Number of patients (n = sample size)	Range of frequency (mean)
Mood and cognitive changes	*Concentration difficulty*	Karli et al. (17)	24.62% (n = 65)	1.75–83.01% (33.78%)	*Apathy/irritability/ petulance*	Karli et al. (17)	1.54% (n = 65)	1.54–42% (20.83%)
		Schoonman et al. (18)	28.1% (n = 374)			Schoonman et al. (18)	28.1% (n = 374)	
		Quintela et al. (19)	36% (n = 100)			Quintela et al. (19)	42% (n = 100)	
		Schulte et al. (7)	~28% (n = 1010)			Schulte et al. (7)	~25% (n = 1010)	
		Karsan et al. (20)	83.01% (n = 53)			Güven et al. (23)	15.9% (n = 339)	
		Ran et al. (21)	1.75% (n = 5438)			Ran et al. (21)	1.49% (n = 5438)	
		Thuraiaiyah et al. (22)	35.0% (n = 632)			Thuraiaiyah et al. (22)	31.8% (n = 632)	
	Mood changes/feeling depressed	Kelman et al. (24)	14.4% (n = 893)	1.14–64.15% (36.09%)	*Anxiety/stressed feeling/ restlessness*	Karli et al. (17)	40% (n = 65)	15.2– 46% (31.15%)
		Karli et al. (17)	58.5% (n = 65)			Schoonman et al. (18)	15.2% (n = 374)	
		Schoonman et al. (18)	17.6% (n = 374)			Quintela et al. (19)	46% (n = 100)	
		Quintela et al. (19)	39% (n = 100)			Laurell et al. (25)	~23% (n = 2219)	
		Schulte et al. (7)	~17% (n = 1010)					
		Karsan et al. (20)	64.15% (n = 53)					
		Ran et al. (21)	1.14% (n = 5438)					
		Laurell et al. (25)	~33% (n = 2219)					
		Schwedt et al. (26)	80% (n = 15)					
	Dysphasia/difficulty speaking/writing	Karli et al. (17)	7.69% (n = 65)	7.69–27% (15.25%)	*Overactivity*	Karli et al. (17)	6.15% (n = 65)	1.18–13% (7.58%)
		Schulte et al. (7)	~10% (n = 1010)			Quintela et al. (19)	13% (n = 100)	
		Quintela et al. (19)	17% (n = 100)			Schulte et al. (7)	~10% (n = 1010)	
		Schwedt et al. (26)	27% (n = 15)			Güven et al. (23)	1.18% (n = 339)	
		Thuraiaiyah et al. (22)	14.6% (n = 632)					
	Euphoria	Karli et al. (17)	10.77% (n = 65)	9–10.77% (9.88%)				
		Quintela et al. (19)	9% (n = 100)					
Sensory sensitivities	*Vertigo/dizziness*	Kelman et al. (24)	0.67% (n = 893)	0.67–67% (21.24%)	*Stiffneck/neckpain*	Kelman et al. (24)	1.5% (n = 893)	1.5–80% (30.91%)
		Karli et al. (17)	38.46% (n = 65)			Karli et al. (17)	29.23% (n = 65)	
		Schulte et al. (7)	~18% (n = 1010)			Schoonman et al. (18)	35.0% (n = 374)	
		Schwedt et al. (26)	67% (n = 15)			Schulte et al. (7)	~29% (n = 1010)	
		Wang et al. (27)	6.9% (n = 4821)			Laurell et al. (25)	~31% (n = 2219)	
		Ran et al. (21)	7.39% (n = 5438)			Schwedt et al. (26)	80% (n = 15)	
		Thuraiaiyah et al. (22)	10.3% (n = 632)			Pradhan et al. (28)	34.3% (n = 391)	
						Wang et al. (27)	6.9% (n = 4821)	
						Karsan et al. (20)	52.83% (n = 53)	
						Ran et al. (21)	8% (n = 5438)	
						Thuraiaiyah et al. (22)	33.2% (n = 632)	
	Phonophobia/sound sensitivity	Kelman et al. (24)	0.7% (n = 893)	0.7–86.15% (30.08%)	*Photophobia/light sensitivity*	Kelman et al. (24)	0.8% (n = 893)	0.8–73% (34.46%)
		Karli et al. (17)	86.15 (n = 65)			Karli et al. (17)	86.15% (n = 65)	
		Schoonman et al. (18)	36.4% (n = 374)			Quintela et al. (19)	37% (n = 100)	
		Quintela et al. (19)	44% (n = 100)			Schulte et al. (7)	~27% (n = 1010)	
		Schulte et al. (7)	~28% (n = 1010)			Laurell et al. (25)	~31% (n = 2219)	
		Laurell et al. (25)	~18% (n = 2219)			Schwedt et al. (26)	73% (n = 15)	
		Schwedt et al. (26)	47% (n = 15)			Karsan et al. (20)	22.64% (n = 53)	
		Karsan et al. (20)	13.2% (n = 53)			Ran et al. (21)	3.2% (n = 5438)	
		Ran et al. (21)	2.89% (n = 5438)			Thuraiaiyah et al. (22)	30.4% (n = 632)	
		Thuraiaiyah et al. (22)	24.5% (n = 632)					
	Nausea	Schoonman et al. (18)	28.6% (n = 374)	7.07–28.6% (20.07%)	*Osmophobia/smell distortion*	Kelman et al. (24)	0.45% (n = 893)	0.45–27% (14.17%)
		Quintela et al. (19)	24% (n = 100)			Schulte et al. (7)	~20% (n = 1010)	
		Schulte et al. (7)	~20% (n = 1010)			Schwedt et al. (26)	27% (n = 15)	
						Karli et al. (17)	9.23% (n = 65)	

(continued)

Table 1. (continued)

Category	Prodromal symptom	Reference	Number of patients (n = sample size)	Range of frequency (mean)	Prodromal symptom	Reference	Number of patients (n = sample size)	Range of frequency (mean)
		Thuraiaiyah et al. (22)	20.7% (n = 632)					
		Güven et al. (23)	7.07% (n = 339)					
	Blurred vision	Kelman et al. (24)	0.7% (n = 893)	0.7–53% (25.23%)	*Sensation cold*	Karli et al. (17)	35.38 (n = 65)	1.4–35.38% (19.19%)
		Laurell et al. (25)	~22% (n = 2219)			Quintela et al. (19)	19% (n = 100)	
		Schwedt et al. (26)	53% (n = 15)			Laurell et al. (25)	21% (n = 2219)	
						Ran et al. (21)	1.4% (n = 5438)	
					Allodynia	Kelman et al. (24)	3.5% (n = 893)	3.5–12% (7.75%)
						Schulte et al. (7)	~12% (n = 1010)	
Homeostatic and hormonal changes	*Yawning*	Kelman et al. (24)	0.3% (n = 893)	0.3–40% (25.74%)	*Food craving/ hunger*	Kelman et al. (24)	0.2% (n = 893)	0.2–40% (20.46%)
		Karli et al. (17)	36.92% (n = 65)			Karli et al. (17)	20% (n = 65)	
		Schoonman et al. (18)	35.8% (n = 374)			Schoonman et al. (18)	17.4% (n = 374)	
		Quintela et al. (19)	40% (n = 100)			Quintela et al. (19)	15% (n = 100)	
		Schulte et al. (7)	~16% (n = 1010)			Laurell et al. (25)	~21% (n = 2219)	
		Laurell et al. (25)	~34% (n = 2223)			Schwedt et al. (26)	40% (n = 15)	
		Schwedt et al. (26)	67% (n = 15)			Karsan et al. (20)	32.07% (n = 53)	
		Güven et al. (23)	21.2% (n = 339)			Thuraiaiyah et al. (22)	18.0% (n = 632)	
		Wang et al. (27)	4.2% (n = 4821)					
		Ran et al. (21)	4.28% (n = 5438)					
		Thuraiaiyah et al. (22)	23.6% (n = 632)					
	Fatigue	Kelman et al. (24)	15.8% (n = 893)	2.81– 77.35% (41.54%)	*Thirst*	Karli et al. (17)	7.69% (n = 65)	7.69–33.96% (15.89%)
		Quintela et al. (19)	38% (n = 100)			Quintela et al. (19)	17% (n = 100)	
		Schoonman et al. (18)	46.5% (n = 374)			Laurell et al. (25)	~8% (n = 2219)	
		Schulte et al. (7)	~25% (n = 1010)			Karsan et al. (20)	33.96% (n = 53)	
		Schwedt et al. (26)	87% (n = 15)			Thuraiaiyah et al. (22)	12.8% (n = 632)	
		Karsan et al. (20)	77.35% (n = 53)					
		Ran et al. (21)	2.81% (n = 5438)					
		Thuraiaiyah et al. (22)	39.9% (n = 632)					
	Diuresis	Karli et al. (17)	16.92% (n = 65)	8.2–33% (17.53%)	*Reduced appetite/ anorexia*	Karli et al. (17)	10.77% (n = 65)	1.88–20% (11.25%)
		Quintela et al. (19)	12% (n = 100)			Quintela et al. (19)	20% (n = 100)	
		Schwedt et al. (26)	33% (n = 15)			Schulte et al. (7)	~10% (n = 1010)	
		Thuraiaiyah et al. (22)	8.2% (n = 632)			Güven et al. (23)	13.6% (n = 339)	
						Ran et al. (21)	1.88% (n = 5438)	
	Sleep disturbance	Schoonman et al. (18)	13.9% (n = 374)	13.9–27% (19.3%)	*Sweating*	Laurell et al. (25)	~9% (n = 2219)	9–67% (28.4%)
		Quintela et al. (19)	27% (n = 100)			Schwedt et al. (26)	67% (n = 15)	
		Schulte et al. (7)	~17% (n = 1010)			Thuraiaiyah et al. (22)	9.2% (n = 632)	
	Face changes (red or pale)	Schulte et al. (7)	~13% (n = 1010)	13–33% (19.7%)	*Fluid retention*	Karli et al. (17)	4.62% (n = 65)	4.62–12% (7.87%)
		Schwedt et al. (26)	33% (n = 15)			Quintela et al. (19)	12% (n = 100)	
		Thuraiaiyah et al. (22)	13.1% (n = 632)			Laurell et al. (25)	~7% (n = 2219)	
	Diarrhea	Karli et al. (17)	6.15% (n = 65)	4–6.15% (5.38%)	*Drowsiness/ lethargy*	Quintela et al. (19)	35% (n = 100)	3.5–35% (17.09%)
		Quintela et al. (19)	4% (n = 100)			Laurell et al. (25)	~32% (n = 2219)	
		Schulte et al. (7)	~6% (n = 1010)			Wang et al. (27)	3.5% (n = 4821)	
	Gastrointestinal symptoms	Kelman et al. (24)	11.8% (n = 893)	11.8–33% (22.4%)		Ran et al. (21)	3.77% (n = 5438)	
		Schwedt et al. (26)	33% (n = 15)			Güven et al. (23)	11.2% (n = 339)	

et al. (15), who showed that 67.6% of the patients were able to predict at least one attack. However, PSs may not be constant in every migraine attack (3,16), and only a minority of subjects can predict consistently more than 50% of attacks (15).

Migraine triggers

Migraine triggers are factors alleged to initiate a sequence of events that culminate in the attack. Stress, sleep deprivation, fatigue, bright lights, odors, menses, noise, skipping meals, weather changes, certain foods and alcohol are among the most reported triggers in clinical studies (Table 2) (17,21,27,29–47). Triggers are important for patients because they want to avoid attacks and therefore they modify behaviors that may facilitate them.

Clinical perspective on migraine attack onset

The ongoing debate revolves around the differentiation of "patient-perceived triggers" and PSs within the framework of a migraine attack. The pivotal issue requiring clarification is whether they represent distinct entities or are the same early manifestations of the onset of a migraine attack (7,20,25,49).

The prevalence of PSs is reported to be in the range 30–80% (18,50). Some PSs (such as yawning and fatigue) are frequently reported during headache and postdrome phases. This observation suggests that the manifestation of these symptoms may precede the onset of migraine pain, can persist throughout the pain phase and further extend into the postdrome (49). Although psychological and emotional changes are commonly encountered in all three phases of the migraine attack, anxiety, mood changes and impatience are more explicit in the prodromal phase (51). The identification of PSs might be more complex regarding patients with a high frequency of attacks, such as subjects with chronic migraine, where the borders between the end of an attack and the beginning of another are blurred. Indeed, the postdrome might overlap with the onset of a new attack in these patients, making it challenging to identify triggers or PSs (52). Additionally, PSs might show variations among distinct subtypes of migraine, with patients with aura having more reported PSs than patients without aura (21,25). By contrast, patients with migraine without aura reported more triggers than those with aura (21).

Regarding migraine triggers, the scientific rationale for establishing a causal connection with headache onset remains insufficient for most of them (29). This is mainly because the data on migraine triggers have been obtained from epidemiological and clinical studies with a wide range of heterogeneity. These include distinctive patient population samples, different methods of collecting data (diary-based, retrospective, prospective, etc.) and various definitions of migraine triggers (Table 3). Most data are based on patient perceptions and observations (49,53,54). Considering that people with migraine could be driven by the desire to comprehend precipitating factors and avoid them, they may falsely associate specific triggers with the initiation of headache.

Indeed, recording triggers with a smartphone application for 90 days, two recent studies observed that individuals with episodic migraine believe that a huge amount of triggers contribute to their attacks, whereas only a few are associated with a real increase in the risk of attacks (55,56). By contrast, patients may fail to identify a genuine yet subtle trigger, highlighting the potential for overlooking triggers that are less overt or conspicuous (53). It is currently unclear whether a trigger can always start an attack if the system is not ready for it, which enhances the complexity between the balance of internal and external stimuli.

Overlap between premonitory symptoms and triggers

A conspicuous overlap appears between some PSs and triggers (Figure 1). It was hypothesized that most of these factors, rather than triggers, can be symptoms of abnormal brain activity during the prodromal phase. Patients might notice the time association with attack onset and consider these factors as triggers rather than the onset of their migraine attack (7). Neck pain, food cravings, and sensitivity to light are the most frequent PSs that might be perceived as triggers (52). Photophobia and phonophobia may cause the perception of lights and sound as unpleasant, leading to the idea that these stimuli could have caused the attacks. Similarly, neck pain is often viewed as a trigger rather than an early symptom of the migraine attack (52).

Additionally, prodrome may lead to behaviors that could be interpreted as triggers. Cravings for specific food might result in consuming certain foods falsely perceived as triggers or might lead to the mistaken belief that skipping meals causes the attacks. Tiredness or sleep deprivation could wrongly be interpreted as the cause of the attack rather than PSs (fatigue and sleep disturbances). Mood changes and irritability may lead to the false interpretation that stress triggers the attack (8).

However, it is important to note that some triggers are consistently reported among different studies, and caution should be exercised in interpreting all triggers as PSs. This could be the case with several well-recognized triggers (6,52), such as stress, tiredness, sleep deprivation, menstruation and fasting, which could have a plausible mechanism in reducing the migraine threshold and could be defined as "catalyst triggers" (see the section below on "How the migraine attack starts: a unifying theory between triggers and prodrome"). By lowering the migraine threshold, the catalyst triggers may speed up the ongoing modifications of the brain networks in the premonitory phase. Therefore, even in a minority of cases, it should be

Table 2. Range of frequency of different migraine triggers in clinical studies (triggers that were investigated by only one study were not reported).

Category of trigger	Trigger	Reference	% of patients (n = sample size)	Range of frequency (mean)	Trigger	Reference	% of patients (n = sample size)	Range of frequency (mean)
Internal triggers	*Stress*	Spierings et al. (43)	84% (n = 38)	24.9–93.59% (67.85%)	*Hormones/menstruation*	Spierings et al. (43)	57% (n = 30)	2.3–68.8% (44.77%)
		Zivadinov et al. (44)	57.8% (n = 720)			Zivadinov et al. (44)	49.4% (n = 720)	
		Karli et al. (17)	75.38% (n = 65)			Karli et al. (17)	58.46% (n = 65)	
		Wöber et al. (45)	66.7% (n = 66)			Wöber et al. (45)	51.4% (n = 61)	
		Hauge et al. (46)	58% (n = 278)			Kelman et al. (6)	65.1% (n = 1750)	
		Kelman et al. (6)	79.7% (n = 1750)			Mollaoğlu et al. (47)	16.6% (n = 126)	
		Mollaoğlu et al. (47)	78.6% (n = 126)			Al-Ashel et al. (34)	2.3% (n = 173)	
		Al-Hashel et al. (34)	24.9% (n = 173)			Constantinides et al. (40)	62.8% (n = 43)	
		Constantinides et al. (40)	52.9% (n = 51)			Iliopoulos et al. (37)	45.45% (n = 88)	
		Iliopoulos et al. (37)	82.95% (n = 88)			Gu et al. (31)	67.21% (n = 78)	
		Gu et al. (31)	93.59% (n = 78)			Chadzynski et al. (36)	66.67% (n = 40)	
		Chadzynski et al. (36)	82.5% (n = 40)			Aljaafari et al. (32)	25% (n = 16)	
		Aljaafari et al. (32)	88% (n = 16)			Ran et al. (21)	9.8% (n = 5438)	
		Karsan et al. (20)	49% (n = 53)			Xie et al. (30)	68.8% (n = 64)	
		Ran et al. (21)	29.97% (n = 5438)			Athar et al. (35)	31.8% (n = 393)	
		Xie et al. (30)	80.7% (n = 83)			Anaya et al. (39)	38.5% (n = 177)	
		Athar et al. (35)	66.7% (n = 393)					
		Anaya et al. (39)	70.0% (n = 177)					
	Dehydration	Hauge et al. (46)	3.59% (n = 278)	3.59–49.9% (26.74%)	*Neck pain*	Hauge et al. (46)	3.23% (n = 278)	3.23–38.4% (20.26%)
		Athar et al. (35)	49.9% (n = 393)			Kelman et al. (6)	38.4% (n = 1750)	
						Lampl et al. (48)	7.4% (n = 487)	
						Pradhan et al. (28)	32% (n = 391)	
	Skipping meals/fasting	Spierings et al. (43)	82% (n = 38)	5.8–82% (39.5%)	*Poor sleep/sleep disturbance*	Spierings et al. (43)	74% (n = 38)	20.8–94% (59.87%)
		Kelman et al. (6)	57.3% (n = 1750)			Zivadinov et al. (44)	40.1% (n = 720)	
		Al-Hashel et al. (34)	5.8% (n = 173)			Karli et al. (17)	52.31% (n = 65)	
		Iliopoulos et al. (37)	34.09% (n = 88)			Kelman et al. (6)	49.8% (n = 1750)	
		Gu et al. (31)	30.77% (n = 78)			Mollaoğlu et al. (47)	63% (n = 126)	
		Chadzynski et al. (36)	65% (n = 40)			Al-Hashel et al. (34)	20.8% (n = 173)	
		Aljaafari et al. (32)	38% (n = 16)			Constantinides et al. (40)	37.2% (n = 51)	
		Karsan et al. (20)	13.2% (n = 53)			Iliopoulos et al. (37)	52.28% (n = 88)	
		Ran et al. (21)	19.76% (n = 5438)			Gu et al. (31)	92.31% (n = 78)	
		Athar et al. (35)	49.1% (n = 393)			Chadzynski et al. (36)	62.5% (n = 40)	
						Aljaafari et al. (32)	75% (n = 16)	
						Karsan et al. (20)	24.52% (n = 53)	
						Xie et al. (30)	94% (n = 83)	
						Athar et al. (35)	70.5% (n = 393)	
						Anaya et al. (39)	89.8% (n = 177)	
	Sleep hours changes	Karli et al. (17)	41.56% (n = 65)	35.23–83.1% (64.04%)	*Fatigue*	Spierings et al. (43)	79% (n = 38)	24.11–79% (54.78%)
		Hauge et al. (46)	57% (n = 278)			Iliopoulos et al. (37)	45.46% (n = 88)	
		Iliopoulos et al. (37)	35.23% (n = 88)			Chadzynski et al. (36)	52.5% (n = 40)	

(continued)

Table 2. (continued)

Category of trigger	Trigger	Reference	% of patients (n = sample size)	Range of frequency (mean)	Trigger	Reference	% of patients (n = sample size)	Range of frequency (mean)
		Gu et al. (31)	87.18% (n = 78)			Ran et al. (21)	24.11% (n = 5438)	
		Xie et al. (30)	83.1% (n = 83)			Xie et al. (30)	63.2% (n = 83)	
		Anaya et al. (39)	80.2% (n = 177)			Athar et al. (35)	64.4% (n = 393)	
External triggers	*Eyestrain/Physiochine activity*	Spierings et al. (43)	50% (n = 38)	2.92–25% (37.5%) (23.61%)	*Weather changes*	Spierings et al. (43)	39% (n = 38)	8.52–81.58% (45.21%)
		Karli et al. (17)	29.08% (n = 20)			Karli et al. (17)	24.62% (n = 28)	
		Kelman et al. (6)	20.0% (n = 275)			Mollaoğlu et al. (47)	82.5% (n = 66)	
		Kelman et al. (6)	38.0% (n = 1750)			Kelman et al. (6)	38.22% (n = 1780)	
		Mollaoğlu et al. (47)	22.6% (n = 126)			Chadzynski et al. (36)	57.5% (n = 40)	
		Mollaoğlu et al. (47)	1.5% (n = 126)			Chadzynski et al. (36)	75% (n = 40)	
		Al-Hashel et al. (34)	26.14% (n = 788)			Kansan et al. (20)	27.5% (n = 853)	
		Ciboduloski et al. (36)	60.25% (n = 40)			Athar et al. (35)	52.7% (n = 393)	
		Aljaafari et al. (32)	25% (n = 16)			Xie et al. (30)	83.6% (n = 87)	
		Kansan et al. (20)	25.28% (n = 5538)			Athar et al. (35)	58.8% (n = 393)	
		Xie et al. (30)	35.3% (n = 83)			Anaya et al. (39)	61.5% (n = 177)	
		Xie et al. (30)	60.4% (n = 893)					
		Anaya et al. (39)	79.2% (n = 177)					
	Traveling	Zivadinov et al. (44)	54.8% (n = 720)	32.95–54.6% (42.48%)	*Heavy lifting/altitudes*	Karli et al. (17)	10.77% (n = 65)	9.09–27.5% (14.14%)
		Iliopoulos et al. (37)	32.95% (n = 88)			Iliopoulos et al. (37)	9.09% (n = 88)	
		Athar et al. (35)	39.9% (n = 393)			Chadzynski et al. (36)	27.5% (n = 40)	
						Athar et al. (35)	9.2% (n = 393)	
	Sexual activity	Karli et al. (17)	6.15% (n = 65)	0–10.22% (4.74%)	*Alcohol intake*	Spierings et al. (43)	42% (n = 38)	1.86–53% (31.57%)
		Kelman et al. (6)	5.2% (n = 1750)			Karli et al. (17)	3.08% (n = 65)	
		Mollaoğlu et al. (47)	0% (n = 126)			Kelman et al. (6)	37.8% (n = 1750)	
		Iliopoulos et al. (37)	10.22% (n = 88)			Mollaoğlu et al. (47)	3.9% (n = 126)	
		Athar et al. (35)	2.3% (n = 393)			Constantinides et al. (40)	25.5% (n = 51)	
							32.95% (n = 88)	
						Iliopoulos et al. (37)	61.54 (n = 78)	
						Gu et al. (31)	35.6% (n = 2197)	
						Onderwater et al. (42)	50% (n = 40)	
						Chadzynski et al. (36)	1.86% (n = 5438)	
						Ran et al. (21)	53% (n = 83)	
						Xie et al. (30)		
	Odors/certain smells or perfume	Spierings et al. (43)	61% (n = 38)	6.16–73.08% (39.93%)	*Hot or cold weather*	Mollaoğlu et al. (47) (cold)	5.5% (n = 126)	5.5–79.49% (39.78%)
		Karli et al. (17)	27.69% (n = 65)				7.1% (n = 126)	
		Kelman et al. (6)	43.7% (n = 1750)			Mollaoğlu et al. (47) (hot)	38.64% (n = 88)	
		Mollaoğlu et al. (47)	17.4% (n = 126)				79.49% (n = 78)	
		Iliopoulos et al. (37)	42.05% (n = 88)			Iliopoulos et al. (37)	15.13% (n = 5438)	
		Gu et al. (31)	73.08% (n = 78)			Gu et al. (31)	67.5% (n = 83)	
		Ran et al. (21)	6.16% (n = 5438)			Ran et al. (21)	65.1% (n = 83)	
		Xie et al. (30)	59% (n = 83)			Xie et al. (30) (cold)		
		Athar et al. (35)	30.8% (n = 393)			Xie et al. (30) (hot)		
		Anaya et al. (39)	38.4% (n = 177)					

(continued)

Table 2. (continued)

Category of trigger	Trigger	Reference	% of patients (n = sample size)	Range of frequency (mean)	Trigger	Reference	% of patients (n = sample size)	Range of frequency (mean)
	Intense emotion	Hauge et al. (46) Iliopoulos et al. (37) Xie et al. (30)	59% (n = 278) 69.32% (n = 88) 61.4% (n = 83)	59–69.32% (63.24%)	*Relaxation after stress*	Wöber et al. (45) Hauge et al. (46) Iliopoulos et al. (37) Chadzynski et al. (36)	50% (n = 66) 70% (n = 278) 29.54% (n = 88) 42.5% (n = 40)	29.54–70% (48.01%)
	Much reading	Spierings et al. (43) Al-Hashel et al. (34)	18% (n = 38) 18.5% (n = 173)	18–18.5% (18.25%)	*Wind*	Hauge et al. (46) Iliopoulos et al. (37) Gu et al. (31)	2.51% (n = 278) 27.27% (n = 88) 60.26% (n = 78)	2.51–60.26% (30.01%)
	Oversleep	Karli et al. (17) Mollaoğlu et al. (47) Iliopoulos et al. (37) Chadzynski et al. (36) Xie et al. (30)	23.08% (n = 65) 33.3% (n = 128) 30.68% (n = 88) 60.0% (n = 40) 62.7% (n = 83)	23.08–62.7% (41.95%)	*Smoking*	Spierings et al. (43) Kelman et al. (6) Mollaoğlu et al. (47) Al-Hashel et al. (34) Iliopoulos et al. (37) Gu et al. (31) Xie et al. (30) Athar et al. (35) Anaya et al. (39)	61% (n = 38) 35.7% (n = 1750) 8.7% (n = 126) 5.8% (n = 173) 23.86 (n = 88) 58.97% (n = 78) 30.1% (n = 83) 8.1% (n = 393) 19.2% (n = 177)	0.6–61% (27.94%)
	Hunger	Karli et al. (17) Hauge et al. (46) Mollaoğlu et al. (47) Iliopoulos et al. (37) Gu et al. (31) Xie et al. (30) Anaya et al. (39)	69.23% (n = 65) 3.95% (n = 278) 53.9% (n = 126) 36.36% (n = 88) 44.87% (n = 78) 49.4% (n = 83) 59.8% (n = 177)	3.95–69.23% (45.35%)	*Head/neck movement*	Karli et al. (17) Mollaoğlu et al. (47) Gu et al. (31) Xie et al. (30)	7.69% (n = 65) 3.1% (n = 126) 60.26% (n = 78) 60.2% (n = 83)	3.1–60.26% (32.81%)
	Coffee	Mollaoğlu et al. (47) Iliopoulos et al. (37) Gu et al. (31) Aljaafari et al. (32) Xie et al. (30) Anaya et al. (39)	18.3% (n = 126) 19.32% (n = 88) 46.54% (n = 78) 19% (n = 16) 47% (n = 83) 32.7% (n = 177)	18.3–47% (30.47%)	*Chocolate*	Iliopoulos et al. (37) Constantinides et al. (40) Gu et al. (31) Xie et al. (30)	19.32% (n = 88) 9.8% (n = 51) 26.92% (n = 78) 16.9% (n = 83)	9.8–26.92% (18.23%)
	Dairy products	Mollaoğlu et al. (47) Constantinides et al. (40) Iliopoulos et al. (37) Gu et al. (31) Xie et al. (30)	10.3% (n = 126) 4.2% (n = 47) 12.50% (n = 88) 33.33% (n = 78) 21.7% (n = 83)	4.2–33.33% (16.41%)	*Food (not specified or combination)*	Spierings et al. (43) Zivadinov et al. (44) Karli et al. (17) Kelman et al. (6) Constantinides et al. (40) Iliopoulos et al. (37) Gu et al. (31) Chadzynski et al. (36) Karsan et al. (20) Anaya et al. (39) Athar et al. (35)	58% (n = 38) 12.5% (n = 720) 30.77% (n = 65) 26.9% (n = 1750) 33.3% (n = 51) 12.5% (n = 88) 14.10% (n = 78) 37.5% (n = 40) 32.07% (n = 53) 19.2% (n = 177) 8.9% (n = 393)	8.9–58% (25.98%)

Table 3. List of clinical studies with the most reported triggers and prodromal symptoms.

Year, reference	Country	Type of study	Sample size (n) and patient cohort	Most common triggers (top 5)	Most common PSs (top 5)
2001, Spierings et al. (43)	USA	Cross-sectional study, telephone interview	n = 38 – MwA/MwoA = nr – F/M = 30/18	– stress/tension, 84% – not eating on time, 82% – fatigue, 79% – lack of sleep, 74% – weather, 71%	Not investigated
2003, Giffin et al. (12)	Denmark, UK, USA	Prospective study with electronic diary	n = 97 – MwA/MwoA = 24/73 – F/M = 92/5 Total diary sessions recorded: 7201 Session with PSs = 803	Not investigated	– tired/weary, 72.5% – concentration difficulty, 51.1% – stiff neck, 49.7% – light sensitive, 48.8% – noise sensitive, 38.4%
2003, Zivadinov et al. (44)	Croatia	Population-based survey	n = 720 (639 active migraine) –MwA/MwoA/MwA + MwoA = 224/355/44 – F/M = 451/269	– stress, 57.8% – frequent travelling, 54.6% – menstrual cycle,49.4% – changes in weather conditions and temperature 49% – sleep disturbances, 40.1%	Not investigated
2004, Kelman et al. (24)	USA	Retrospective analysis	n = 893 – MwA/MwoA = nr – F/M = 760/133 – n of pts with PSs = 29.3%	Not investigated	– fatigue, 15.8.% (% of total pts) – mood change, 14.4% – GI symptoms, 11.8% – head pain/aching/twitching, 3.5% – eye symptoms, 2.0%
2005, Karli et al. (17)	Turkey	Cross-sectional study, questionnaire-based	n = 96 – MwA/MwoA = 23/33 – TTH = 31 – TANMH = 9 – F/M = 83/13	– anxiety, 75.38% – hunger, 69.23% – menstruation, 58.46% – sleeplessness, 52.31% – weather changes, 44.62%	– photophobia, 86.15% – phonophobia, 86.15% – depressive symptoms, 58.46% – restlessness, 40% – dizziness, 38.46%
2006, Schoonman et al. (18)	Netherlands	Cross-sectional study, questionnaire-based	n = 374 – MwA/MwoA = 185/179 – F/M = 300/74	Not investigated	– fatigue, 46.5% – phonophobia, 36.4% – yawning, 35.8% – stiff neck, 35.0% – nausea, 28.6%
2006, Quintela et al. (19)	Spain	Prospective study	n = 100 – MwA/MwoA = 15/85 – F/M = 82/18	Not investigated	– anxiety, 46% – phonophobia, 44% – irritability, 42% – yawning, 40% – unhappiness, 39%
2006, Wöber et al. (45)	Austria	Cross-sectional study	n = 66 – MwA/MwoA = nr – F/M = 61/5	– weather, 82% – stress, 66.7% – menstruation, 51.4% – relaxation after stress, 50% – hunger,	Not investigated

(continued)

Table 3. (continued)

Year, reference	Country	Type of study	Sample size (n) and patient cohort	Most common triggers (top 5)	Most common PSs (top 5)
2007, Kelman (6)	USA	Retrospective analysis	n = 1750 – MwA/MwoA = nr – EM/CM/probable migraine = 716/491/543 – F/M = 1475/275	– stress, 79.7% – hormones, 65.1% – not eating, 57.3% – weather, 53.2% – sleep disturbance, 49.8%	Not investigated
2011, Hauge et al. (46)	Denmark	Cross-sectional study, questionnaire-based	n = 347 – MwA/MwoA = nr – F/M = 215/132	– relaxation after stress, 70% – bright light, 61% – intense emotional influences, 59% – acute stress (during stress), 58% – sleeping too much/little, 57%	Not investigated
2013, Mollaoğlu et al. (47)	Turkey	Cross-sectional study, questionnaire-based	n = 126 – MwA/MwoA = 53/73 – F/M = 86/40	– stress, 78.6% – lack of sleep, 63.5% – hunger, 53.9% – changes in time of sleep, 35.7% – oversleep, 33.3%	Not investigated
2014, Al-Hashel et al. (34)	Kuwait	Cross-sectional study, questionnaire-based	n = 173 – MwA/MwoA = nr – F/M = 136/37	– stress, 24.9% – irregular sleep, 20.8% – substantial reading, 18.5% – exams, 11.1% – smoking 5.8% – fasting, 5.8%	Not investigated
2015, Constantinides et al. (40)	Greece	Cross-sectional study	n = 63 – MwA/MwoA = 12/39 – TTH = 12 – F/M = 54/9	– menses, 63% – stress, 53% – insomnia, 37% – food, 33% – alcohol, 27%	Not investigated
2015, Lampl et al. (48)	Austria	Prospective study, self-filled questionairre	n = 487 – MwA/MwoA = 112/375 – F/M = 356/131	Not investigated	– neck pain, 7.4% Other PSs were not investigated
2015, Schulte et al. (7)	Germany	Retrospective cohort questionnaire-based study	n = 1010 – MwA/MwoA = 311/699 – F/M = 829/181	Not reported	– tense neck – phonophobia – difficulty concentrating – exhaustion – fatigue
2015, Iliopoulos et al. (37)	Greece	Cross-sectional study	n = 116 – MwA/MwoA = 41/47 – TTH = 28 – F/M = 93/23	– stressful life events, 83.62% – intense emotions, 70.69% – lack of sleep, 50.86% – fatigue, 47.41% – weather changes, 46.55%	Not investigated
2016, Laurell et al. (25)	Finland	Cross-sectional study, questionnaire-based	n = 2219 – MwA/MwoA = 1188/1031 – F/M = 1744/475	Not investigated	– yawning, ~34% – mood change, ~33% – lethargy, ~32%

(continued)

Table 3. (continued)

Year, reference	Country	Type of study	Sample size (n) and patient cohort	Most common triggers (top 5)	Most common PSs (top 5)
					– neck symptoms, ~30% – light sensitivity, ~30%
2016, Park et al. (38)	Korea	Prospective study, smartphone headache diary	n = 62 – MwA/MwoA = 2/60 – F/M = 51/11	– stress, 36% – sleep deprivation, 24% – fatigue, 22,3% – hormonal changes, 18.5% – weather changes, 8%	Not investigated
2018, Schwedt et al. (26)	USA	Prospective longitudinal observational study	n = 15 – MwA/MwoA = 0/15 – F/M = 13/2	Not investigated	– generalized feeling of being unwell, 87% – fatigue/tiredness, 87% – mood change, 80% – neck stiffness, 80% – light sensitivity, 73%
2018, Gu et al. (31)	China	Cross-sectional study, self-administered questionnaire	n = 986 – MwA/MwoA = nr – F/M = 620/366	– stress at study or work, 93.6% – lack of sleep, 92.3% – change in time of sleep, 87.2%	Not investigated
2018, Pradhan et al. (28)	India	Prospective observational study	n = 391 – MwA/MwoA = 68/323 – F/M = 166/102	– neck pain, 32% Other triggers were not investigated	– neck pain, 34.3% Other PSs were not investigated
2018, Gago-Veiga et al. (15)	Spain	Prospective observational study	n = 34 – MwA/MwoA = 19/15 – F/M = 30/34	Not investigated	– photophobia, 29.6% – drowsiness, 23.5% – fatigue, 20.9% – yawning, 19.6% – phonophobia, 19.6%
2018, Güven et al. (23)	Turkey	Prospective study, questionnaire and headache diaries	n = 339 – MwA/MwoA = 131/208 – F/M = 301/38	Not investigated	– yawning, 21.2% – irritability/anxiety, 15.9% – changes in appetite, 13.6% Only dopaminergic-hypothalamic PSs were investigated
2019, Onderwater et al. (42)	Netherlands	Cross-sectiona study, web-based, questionnaire	n = 2197 – MwA/MwoA = 851/1346 – F/M = 1887/ 310	– alcohol, 35.6% Other triggers were not investigated	Not investigated
2019, Chadzynski et al. (36)	Poland	Cross-sectional study	n = 80, – MwA/MwoA = 2/34 – CM = 4 – HC = 40 – F/M = 40/0	– stress, 82,5% – sudden weather changes, 75% – menstruation, 66.67% – fasting, 65% – bright light, 62.5%	Not investigated
2021, Wang et al. (27)	China	Multi-center electronic structured questionnaire	n = 4821 – MwA/MwoA = 714/4107 – F/M = 3762/1059	Not reported	– neck stiffness, 6.9% – dizziness, 6.9% – yawning, 4.2% – drowsiness, 3.5%
2021, Aljaafari et al. (32)	Saudi Arabia	Cross sectional descriptive study	n = 16	– study-related stress, 88% – emotional-related stress, 81%	Not investigated

(continued)

Table 3. (continued)

Year, reference	Country	Type of study	Sample size (n) and patient cohort	Most common triggers (top 5)	Most common PSs (top 5)
			– MwA/MwoA = nr – F/M = 11/5	– sleep disturbance, 75% – bright lights, 44% – noise, 44%	
2021, Karsan et al. (20)	UK	Two-part study: retrospective and prospective	n = 53 – MwA/MwoA = 27/20 – F/M = 44/9	– stress, 49% – light, 45% – certain foods, 32% – sound, 23% – dehydration, 19%	– concentration difficulty, 83% – fatigue, 77% – mood change, 64% – neck stiffness, 53%
2022, Ran et al. (21)	China	Cross-sectional, multicenter, electronic survey	n = 5438 – MwA/MwoA = 787/4651 – F/M = 4253/1185	– stress, 29.97% – tiredness, 24.11% – sleep disturbance, 19.76% – hot or cold, 15.13% – hormones (menstruation or pregnancy), 9.8%	– stiff neck, 8.00% – dizziness, 7.39% – yawning, 4.28% – photophobia, 3.2% – phonophobia, 2.89%
2022, Xie et al. (30)	China	Cross-sectional study, self-administered questionnaire	n = 83 – MwA/MwoA: nr – F/M = 64/19	– lack of sleep, 94.0% – change in sleep schedule, 83.1% – noise, 81.9% – academic stress, 80.7% – fatigue, 80.7%	Not investigated
2022, Athar et al. (35)	Pakistan	Cross– sectional study, online survey	n = 393 – MwA/MwoA = nr – F/M = 307/86	– sleep disturbance, 70.5% – stress, 66.7% – fatigue, 64.4% – excess screen time, 61.1% – loud noise, 58.8%	Not investigated
2022, Anaya F et al. (39)	Palestine	Cross-sectional study, self-administered questionnaire	n = 806 – Migraine = 177 (MwoA/MwA: nr) – TTH = 482 – Unclassifiable = 75 – F/M = 476/330	– sleep deprivation, 89.8% – altered sleep pattern, 80.2% – physical activities, 75.7% – stress, 70.0% – long study hours, 70.0%	Not investigated
2024, Thuraiaiyah et al. (22)	Denmark	Cross-sectional study	n = 632 – MwA/MwoA = 199/621 – EM/CM = 251/381 – F/M = 563/69	96% reported trigger factors	– tiredness, 39.9% – difficulty concentrating, 35% – neck pain, 33.2% – irritability, 31.8% – photophobia, 30.4%

Abbreviations: CM = chronic migraine; F = female; GI = gastrointestinal; HC = healthy controls; M = male; MwA = migraine with aura; MwoA = migraine without aura; nr = not reported; PSs = prodromal symptoms; pts = patients; TTH = tension type headache; TANMH = typical aura with non-migraine headache.

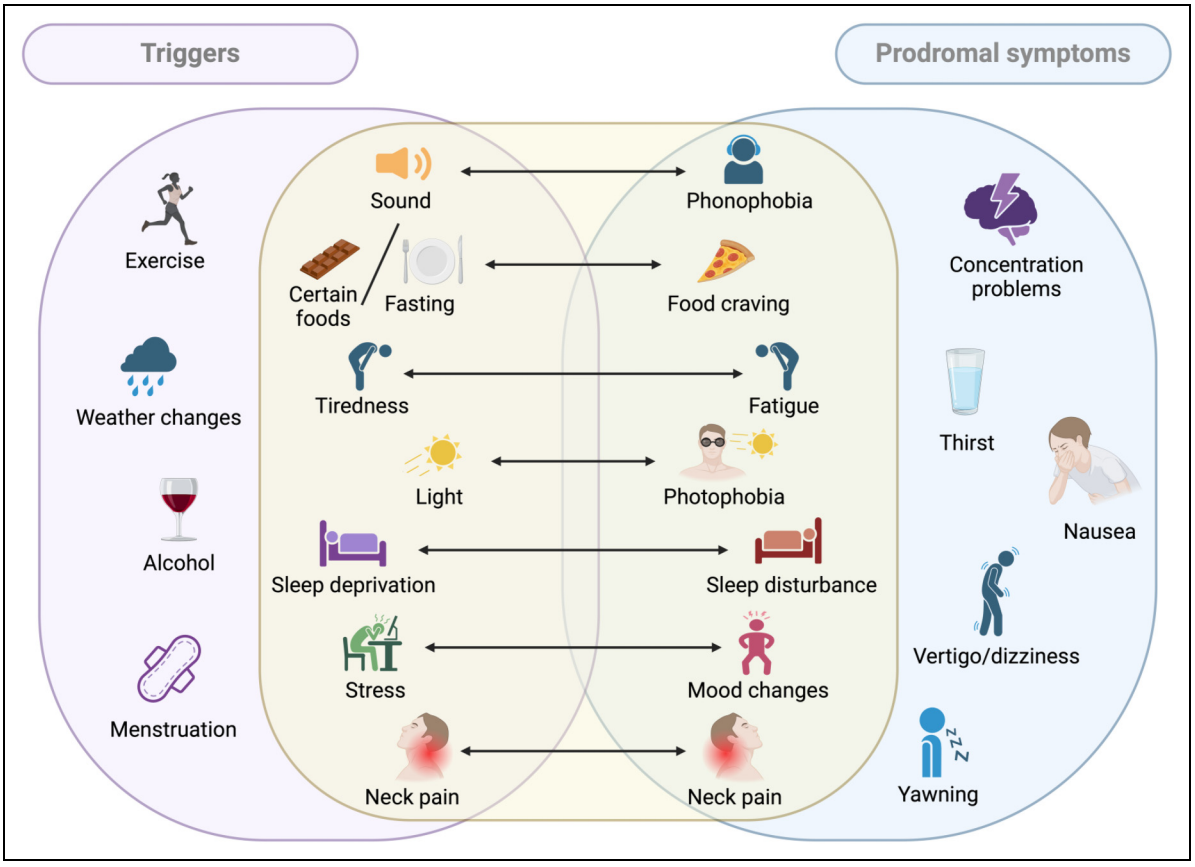

Figure 1. Common triggers (in purple) and prodromal symptoms (in light blue) with potential correlation/overlap between them (in yellow). Created with BioRender.com.

hypothesized that the relationship between triggers and prodrome may be bidirectional, with some triggers acting as true triggers and not just as PS.

Current limitations

As a result of this considerable overlap, the discrimination between some triggers and PSs can be challenging (7) and several methodological issues further hamper this distinction (49,54). First, the number of prospective studies is limited, and considering that reported sensations and symptoms are patient-perceived, most data are prone to recall bias.

Secondly, a standardized and optimized method for assessing PSs is lacking. A recent cross-sectional study found that directly prompting PSs during medical interviews can influence the number of reported symptoms. It was shown that prompted enquiry resulted in a higher proportion of reported PSs (69.9 vs. 43.0%) and higher symptom counts than unprompted enquiry (22). Lastly, just a handful of evidence-based data regarding experimental, imaging and genetic studies focused on distinguishing between these two entities (49).

Studies with provocative molecules can be a reliable and standard model for investigating triggers and PSs. However, most current studies are limited by not conducting repeat tests on the same patient. Large-scale, prospective and standardized methods for assessing PSs and triggers are needed and constitute a prerequisite to estimating their actual prevalence and understanding how they contribute to the onset of migraine attacks.

Pathophysiological perspective on migraine attack onset

Peripheral and central nervous system mechanisms have been continuously investigated over the years aiming to understand what is the *primum movens* of a migraine attack; however, this is still an unresolved question (16). Regardless of the activation source, it is demonstrated that meningeal nociceptors have to be activated to initiate migraine pain, making the trigeminovascular system the final common pathway in starting the headache phase (57).

Prodromal phase

The presence of the pain makes the headache phase the most recognizable by the patients, and this has led to a precise time definition of its duration. The other phases of the migraine

attack are less well-defined because the patients are not fully aware of them. This makes studies focusing on patients' perceptions of PSs susceptible to bias. Indeed, studies focusing on the time onset of the PSs reported different and variable time windows (12,24,58). In a minority of migraine attacks, the prodromal phase may cover up to 72 hours before the headache phase (12). However, the current time definition of the prodromal phase given by the International Classification of Headache Disorders, 3rd edn (ICHD-3) is up to 48 hours, and this appears to be justified by several electrophysiological and neuroimaging evidence (10). An increasing number of studies provide evidence that the hypothalamus may play a crucial role in the prodromal phase (59–61), and its activation was shown up to 48 hours before headache onset but not earlier (62), regardless of the presence of the aura (61). Some PSs, including yawning, food cravings, homeostatic regulation, and sleep disturbance, may be linked to hypothalamus activation (3,63). On the other hand, several brainstem areas become activated during the prodromal phase (59,60) and could be responsible for other PSs, such as neck pain and nausea (64,65). Indeed, patients who experienced nausea as a PS have increased activation in the periaqueductal grey (PAG) and the rostral dorsal medulla. The rostral dorsal medulla includes the nucleus tractus solitarius, which is considered to be involved in circuits that mediate nausea (65) and has connections with the hypothalamus (66) and the trigeminovascular neurons (67). These distinct neuroanatomical pathways could be responsible for nausea as a PS and nausea during the headache phase.

Other brain areas, including the visual cortex (59,60,65) and several pain and limbic regions (68), have been shown to become activated before the pain develops and could be putatively associated with other PSs. Patients who experience photophobia during the prodromal phase have a higher activation of the extrastriate visual cortex than those without photophobia (69). This suggests that photic hypersensitivity (aversion to light without increased pain) is linked to visual cortex activation and is not dependent on trigeminal activation or pain (69). Similarly, sensory sensitivities (photo-phonophobia and allodynia) and changes in mood and cognition (3) could also arise from the activation of thalamocortical connections and functional reorganization of different sensory pathways (63,70–72). Indeed, the thalamus, pons, and limbic areas have been found to change their connectivity when patients experience PSs (73). The prodromal symptoms and possible brain areas involved in their generation are shown in Figure 2.

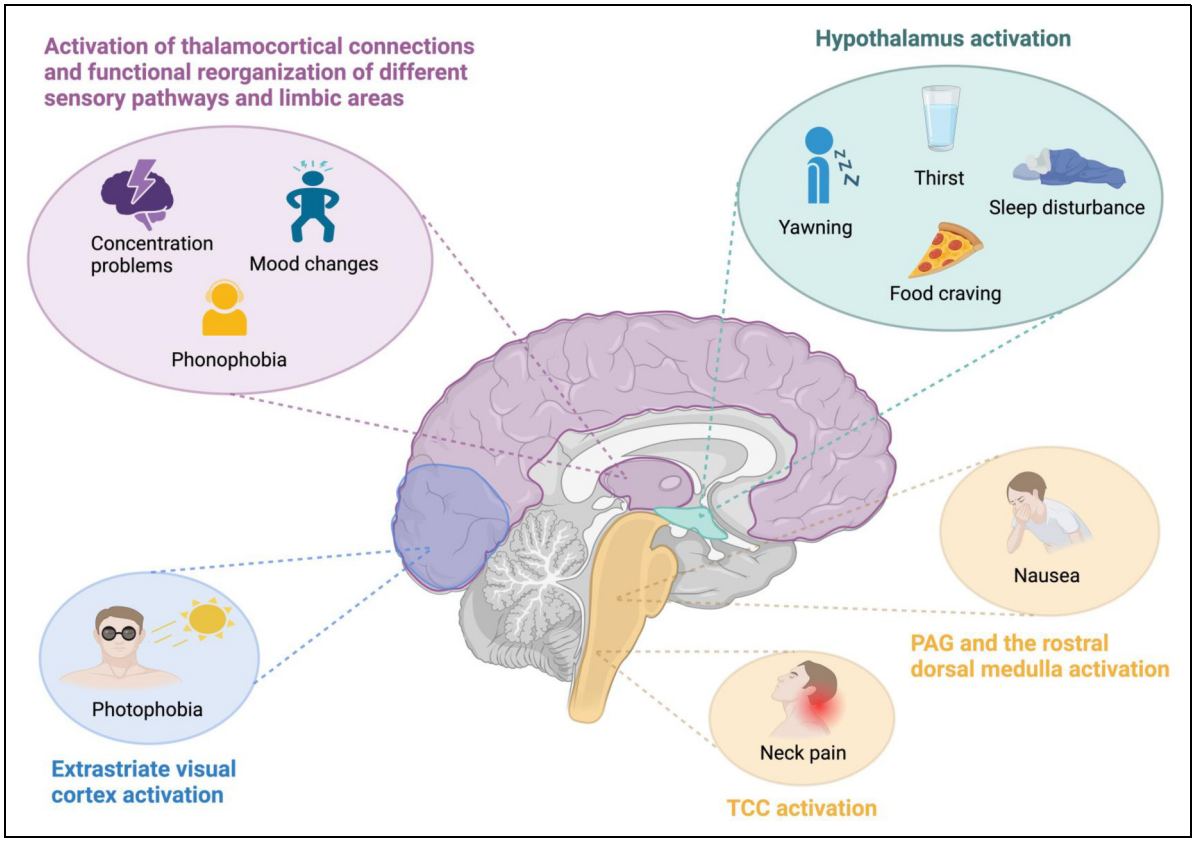

Figure 2. Prodromal symptoms and possible brain areas involved in their generation.
Abbreviations: PAG = periacqueducatl gray; TCC = trigemino-cervical complex. Created with BioRender.com.

Changes in connectivity have been shown to occur cyclically in several brain areas during the migraine cycle (62,74), including the brainstem (75,76), hypothalamus (59), thalamus (77,78), limbic areas (78,79), somatosensory (80–83) and visual cortex (84–86).

Particularly, the changes in connectivity between the hypothalamus and brainstem areas, including the spinal trigeminal nucleus and dorsal rostral pons, are suggested to play a crucial role in driving the different phases of the migraine cycle (59). Furthermore, during the prodromal phase, positive functional coupling was shown between the thalamus and several pain areas (73,78), including the insula, pons, cerebellum, precuneus and cuneus, as well as an increase in connectivity between limbic areas and the hypothalamus (79).

In line with neuroimaging studies, neurophysiological studies provided evidence of fluctuations in central and peripheral functions over the migraine cycle that are accompanied by changes in sensory thresholds, including alterations in pain perception, as well as modifications in sensitivity to light, sound and smell (87–89), confirming that migraine is a cyclical disorder (90). However, brain activity tends to change particularly before the onset of the headache phase, with increased excitability and loss of inhibitory control several hours before the ictal phase (80,82,83,90–95). Cortical processing of sensorimotor (80–83) and visual stimuli (84–86) showed excessive excitation in the immediate pre-migraine phase (80,83,86,90). During the 24 hours preceding the headache onset, the somatosensory excitability tends to reach its maximum in the primary somatosensory cortex and the brainstem (76), which also increases its oscillatory activity (96), particularly in regions that process the pain signals arising from the head (spinal trigeminal nucleus and dorsal pons) (75).

The relevant question is whether migraine triggers may influence these intrinsically generated fluctuations leading to an attack.

Migraine attack triggers

There are several questions here. How easy is it for a trigger to start an attack? How many triggers are needed to start an attack? In an individual, does a single trigger always facilitate an attack? All of this is based on understanding the attack as a headache phase and not on navigating through the presence or absence of certain symptoms. Pathophysiologically, the control of brain and bodily activity can be unbalanced by many different controlling switches. In attacks, more than one trigger might be present (Figure 3).

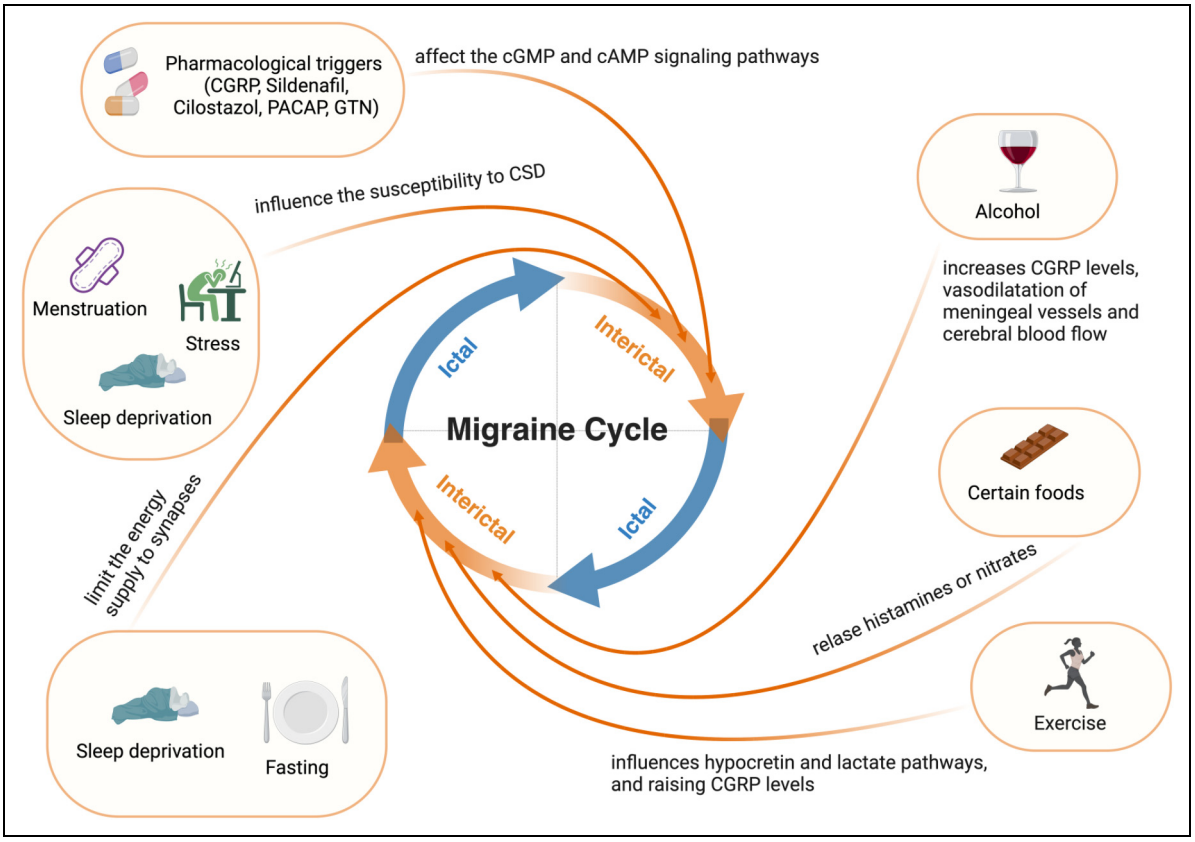

Figure 3. Common migraine triggers and their influence on the migraine cycle.
Abbrevations: CGRP = calcitonin gene-related peptide; CSD = cortical spreading depression; PACAP = pituitary adenylate cyclase-activating polypeptide-38; GTN = glyceryl trinitrate. Created with BioRender.com.

Pharmacological triggers: provocative models

Different experimental models of migraine in humans have been studied over the years, helping to understand the direct pathophysiological and chronological link between a substance and the presence of an attack. These provocative studies have provided evidence about the molecules and pathways involved in migraine pathophysiology (97). Among them, glyceryl trinitrate (GTN), sildenafil, cilostazol, calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating polypeptide-38 (PACAP) infusion are the most utilized and were shown to trigger migraine-like attacks effectively (97). Hypoxia could be another promising model for provocation studies in migraine with aura because it has been shown to trigger migraine-like headaches in healthy volunteers (98), with a more significant proportion of induced attacks than GTN (99). All these provocative models appear to induce migraine by affecting the cGMP and cAMP signaling pathways (97). The ability to successfully trigger migraine attacks has increased the experimental study of migraine in humans, providing a unique opportunity to understand what happens before the onset of pain. It is worth noting that even experimentally triggered migraine-like attacks tend to follow a similar chronological sequence of symptom development, with PSs appearing first (100–102). These studies have confirmed that the trigeminovascular system can be activated, and therefore migraine attacks can be initiated by factors external to the nervous system itself.

Non-pharmacological triggers: internal and external triggers

Non-pharmacological triggers could be ideally divided into internal and external triggers. Internal triggers can be defined as factors associated with the modification of the internal homeostasis state (8). Stress, hormones, sleep deprivation and fasting are among the most reported internal triggers (6). These triggers can increase the chance of a migraine attack by directly disrupting the sensation of the body's internal physiological state (i.e. interoception), which is different between the ictal and interictal phases with prevalent sensory and autonomic changes in the peri-ictal phase (103,104).

By contrast, external triggers are factors or stimuli originating from outside the body that could influence exteroception, which is the perceptual inference based on external sensory signals (105). These include alcohol, bright lights, intensive exercise or certain foods (8) (Table 2). However, these factors are variably reported as migraine triggers, making their role in causing migraine attacks less direct/straightforward than that of internal triggers (6). Both types of triggers were studied with several modalities, and different animal models have been widely used in preclinical studies to understand how some of them may influence the cortical spreading depression (CSD) threshold and, consequently, migraine attack susceptibility. Indeed, a direct link between the CSD and the trigeminovascular system was found in animal models (106). It was shown that CSD can directly activate the trigeminovascular neurons in the trigeminal ganglion (107) and spinal trigeminal nucleus caudalis (STN), playing a role in the onset of migraine pain (108).

Internal triggers: stress, hormones, sleep deprivation and fasting

Cortisol is the predominant adrenal stress hormone in humans, whereas corticosterone is the main corticosteroid hormone in rodents and is the preferred hormone for studying stress responses in animal models (109). In the animal model, the stress hormone corticosterone can increase neuronal excitability and lower the threshold of CSD (110), whereas contrasting results emerged from studying the effects of different stress conditions (111–113). Interestingly, Balkaya et al. (112) found that chronic stress may reduce the CSD threshold only when followed by a period of relief, which could provide a biological basis for the occurrence of migraine attacks during the weekends or holidays (114).

Ovarian hormones also increase the susceptibility to CSD (115,116), whereas androgen hormones were found to have opposite effects (117). However, rather than estrogen itself, it appears that estrogen withdrawal plays a pivotal role with respect to increasing the frequency of CSD (118). Accordingly, it was found that stress may influence the levels of cortical excitability, particularly during the premenstrual period of individuals with migraine (119). This suggests that stress occurring during this period may increase the likelihood of a migraine attack (119). Estrogen withdrawal can also directly influence the sensitization of the trigeminal system in animal models (120). These findings are consistent with the evidence indicating that hormonal changes in female migraine patients can increase CGRP release from the trigeminovascular system, potentially contributing to susceptibility to migraine attacks (121).

Sleep deprivation and fasting are among the most frequently reported triggers by subjects with migraine (6). The role of fasting in triggering migraine has also been demonstrated in several studies conducted during fasting, which showed a worsening of migraine frequency and severity during this period (122–124). In animal models, insufficient glycogen-derived energy substrate supply to synapses or sleep deprivation lowers the CSD threshold. Interestingly, the CSD susceptibility could be reversed by supplementing with an alternate energy source (glucose or lactate). This suggests that both sleep deprivation and fasting may predispose to migraine attacks by limiting the energy supply to synapses (125). Additionally, sleep

deprivation may predispose to migraine attacks by lowering the CSD threshold (125) and through GABA modulation (126,127).

External triggers: alcohol, foods, exercise and visual stimulation

Alcohol is frequently reported as a migraine trigger and is one of the most reported external triggers (6,27,33,38,40–42,128). Red wine is the most reported trigger among alcoholic beverages, although it consistently led to an attack in only a minority of patients (42). This suggests that the ability of alcohol to trigger headache may depend on fluctuating trigger threshold (42). Furthermore, a dose effect for alcohol as a migraine trigger appears to exist. Consuming three or more servings of alcoholic beverages may increase the risk of experiencing a headache the following day, whereas consuming one or two drinks does not appear to increase this risk (41). Several theories have been proposed to explain how alcohol may trigger migraine attacks (129). These include the activation of neurogenic inflammation in the trigeminovascular system via the release of CGRP and the vasodilatation of meningeal vessels (130), as well as its ability to increase cerebral blood flow (131,132). However, the exact mechanism is still unknown (129).

Several studies investigated the ability of certain foods that contain histamines (133) or nitrates (134), such as dairy, chocolate or preserved meat, to provoke headache. However, inconsistent results emerged from these studies (40,135–137). For example, a double-blind provocative study showed no difference between chocolate and carob (used as a placebo) in triggering headache, downsizing the patient-perceived role of chocolate as an actual trigger of migraine attacks (137).

Visual stimulations and physical activity were frequently investigated in humans but with inconsistent results in triggering aura. Indeed, various studies have employed visual stimulation to induce aura in subjects with migraine, with a total trigger rate of 30% (138). Hougaard et al. (139) found that photostimulation and strenuous exercise were able to trigger migraine aura only in a small subgroup of patients, and none of the patients developed migraine after exposure to photostimulation alone. This could be because, for sensory stimulation alone, as demonstrated by intense photic or whisker stimulation in animal models, predisposing factors are required for CSD to be ignited (140).

It should be noted that exercise has been shown to have a double role in migraine (141). Regular exercise may reduce the migraine frequency (142,143), whereas low levels of physical activity were correlated with a high frequency of migraine days (144,145). On the other hand, intense exercise has been reported as a potential trigger in some individuals with migraine (6,139,146,147). However, the number of experimental studies investigating exercise as a migraine trigger is relatively limited, and exercise was shown to trigger migraine in a subgroup of patients (139,146,147). Different mechanisms are suggested to explain how exercise can trigger migraine attacks, such as influencing the hypocretin pathway (147), altering lactate metabolism (148), and raising CGRP levels (149,150).

How the migraine attack starts: a unifying theory between triggers and prodrome

It is worth noting that, although few studies have investigated patients focusing on their PSs and, most of all, with different time definitions of the prodromal phase, neuroimaging studies have identified similar brain regions that become activated during the days before the headache phase (Table 4). As mentioned before, the changes in brain activity were shown to start from hours to days before the headache onset (80,82,83,90), suggesting that the prodromal phase occurs even in the absence of the PSs.

From a pathophysiological perspective (Table 5), the prodromal phase is characterized by increased excitability (80,82,83,90,94,95) and changes in connectivity within interconnected brain networks (5,151). This hyperexcitatory state during the prodromal phase can be hypothesized as the common link between triggers and prodrome.

Considering that the hypothalamus is the principal hub for modulation and integration between external factors, it is a potential candidate for integrating migraine triggers and internal bodily signals (5). Additionally, the hypothalamic–thalamic–brainstem connections and their connectivity changes can influence cortical excitability and the threshold for the migraine attack (152). Indeed, trigeminovascular thalamic neurons receive direct projections from the hypothalamus (72) and are continuously influenced by modulatory inputs based on changes in homeostasis (63). This enables the thalamus to dynamically regulate the transmission of sensory signals, facilitating the adjustment of the cortex to changing physiological, behavioral and environmental demands (153).

The functional reorganization of various pathways between the thalamus and the cerebral cortex during the prodromal phase (73) can impair the sensory filter function of the thalamus (90). This can affect the regulation of the cortex excitability and cause a widespread enhanced activation of different cortical and subcortical brain regions (90). When the excitation level reaches a critical point, the hypothalamus and brainstem areas undergo changes in their connectivity driving the transition from the prodromal to the ictal phase (59). These changes finally activate the trigeminovascular system, which facilitates pain processing and leads to the headache phase (3) (Figure 4(a)).

Table 4. List of neuroimaging studies that investigated the prodromal phase and prodromal symptoms.

Year, reference	Design	Sample size (n)	Methods	Definition of the Preictal / Premonitory Phase	Premonitory symptoms	Provocative	Main findings in the preictal phase
2014, Maniyar et al. (60)	Observational study	– MwoA, n = 8	$H_2^{15}O$ PET	Symptom criteria: the period after the nitroglycerin-induced non-specific headache phase has ceased, and patients experience warning symptoms of an impending headache	Reported	NTG-induced attacks	Activation in the early premonitory phase of the posterolateral hypothalamus, midbrain tegmental area, periaqueductal grey, dorsal pons, and several cortical areas, including occipital, temporal and prefrontal cortex Persistence of activation during the late premonitory phase in the dorsal pontine, but not in the hypothalamus and midbrain. There was also activation in the right pulvinar and left thalamic area
2014, Maniyar et al. (69)	Observational study	– MwoA, n = 10 (5 with photophobia as a premonitory symptom and 5 without photophobia)	$H_2^{15}O$ PET	Symptom criteria: the period after the nitroglycerin-induced non-specific headache phase has ceased, and patients experience warning symptoms of an impending headache	Reported	NTG-induced attacks	Greater activation of extrastriate visual cortex in patients with photophobia as a premonitory symptom, in comparison to patients without photophobia
2014, Maniyar et al. (65)	Observational study	– MwoA, n = 10 (3 with nausea as a premonitory symptom and 7 without nausea)	$H_2^{15}O$ PET	Symptom criteria: the period after the nitroglycerin-induced non-specific headache phase has ceased, and patients experience warning symptoms of an impending headache	Reported	NTG-induced attacks	Activation in rostral dorsal medulla and periaqueductal grey (PAG) in patients with nausea as a premonitory symptom, whereas there is no activation of these areas in the group without nausea
2016, Schulte et al. (59)	Longitudinal observational study (30 days)	– MwoA, n = 1	fMRI	Time criterion: <24 h before headache onset	Not reported	Spontaneous migraine attacks	Hypothalamus activation with functional coupling with the spinal trigeminal nuclei
2018, Meylakh et al. (96)	Observational study	MwoA + MwA, n = 26 (21/5) (preictal recordings = 8) -HC, n = 78	fMRI	Time criterion: <24 h before headache onset	Not reported	Spontaneous attacks	Increase in infraslow oscillatory activity and functional coupling between brainstem and hypothalamic regions in the 24 h before the migraine attack
2020, Schulte et al. (74)	Longitudinal observational study (30 days)	-MwoA + MwA, n = 8 (7/1)	fMRI	Time criterion: Pre 3, Pre 2, Pre 1: 3-2-1 days preceding headache onset	Not reported	Spontaneous attacks	Enhanced functional connectivity of the right nucleus accumbens with the left amygdala, hippocampus, and gyrus parahippocampalis and between the right accumbens and the dorsal rostral pons in the preictal phase
2020, Schulte et al. (62)	Longitudinal observational study (30-days)	– MwoA + MwA, n = 7 (6/1)	fMRI	Not defined	Not reported	Spontaneous migraine attacks	Hypothalamic activation during the 48 h preceding headache onset but not earlier

(continued)

Table 4. (continued)

Year, reference	Design	Sample size (n)	Methods	Definition of the Preictal / Premonitory Phase	Premonitory symptoms	Provocative	Main findings in the preictal phase
2020, Karsan et al. (73)	Randomized, double-blind, placebo-controlled, multi-visit experimental study	– MwoA + MwA, n = 25 (10/15)	fMRI	Symptom criteria: at least 3 typical premonitory symptoms in the absence of headache pain	Reported	NTG-induced attacks	Positive functional coupling between the thalami bilaterally and the right precuneus and cuneus regions during the nitroglycerin-triggered premonitory phase. The nitroglycerin-triggered premonitory phase was associated with a change in the direction of connectivity from positive to negative between the pons and the limbic lobe
2021, Stankewitz et al. (79)	Longitudinal intra-individual study	– MwoA + MwA, n = 12 (9/3) (9 preictal recording)	fMRI with pCASL	Not defined: all subjects had their final recording within 48 h before the subsequent attack	Not reported	Spontaneous attacks	Hypothalamic connectivity to the limbic system increases over the interictal interval towards the attack, then collapses during the headache phase
2021, Martinelli et al. (78)	Observational study	-MwoA, n = 5	fMRI	Symptom criterion: at least 2 premonitory symptoms typical of an NTG triggered migraine-like headache	Reported	NTG-induced attacks	Functional connectivity changes between the right thalamus and areas involved in the pain circuits (insula, pons, cerebellum) during the prodromal phase, reaching its maximal alteration during the headache phase
2021, Meylakh et al. (75)	Longitudinal study (20 days, from Monday to Friday over four weeks)	– MwoA, n = 3 (preictal recording = 5) -HC, n = 5	fMRI	Time criterion: no clear definition	Not reported	Spontaneous attacks	Increase variability in the 24 h before the headache phase in brainstem regions that process head pain (spinal trigeminal nucleus and dorsal pons)
2023, Mehnert et al. (61)	Longitudinal observational study (30 days)	– MwA, n = 1	fMRI	Time criterion: <2 days before headache onset	Not reported	Spontaneous attacks	Activation of the hypothalamus in the preictal phase of attacks with aura and without aura
2023, Karsan et al. (68)	Double-blind placebo-controlled randomized study	-MwoA, n = 12	fMRI with 3D pCASL	Symptom criteria: at least 3 typical premonitory symptoms in the absence of headache pain	Reported	NTG-induced	Increase in CBF in several regions, including anterior cingulate cortex, caudate, midbrain, lentiform, amygdala, hypothalamus, and hippocampus during nitroglycerine induced premonitory symptoms

Abbreviations: CBF = cerebral blood flow; fMRI = functional magnetic resonance imaging; GTN = glyceryl trinitrate; h = hours; HC = healthy control; MRS = magnetic resonance spectroscopy; MwA = migraine with aura; MwoA = migraine without aura; NTG = nitroglycerin; pCASL = pseudo-continuous arterial spin labelling; PET = positron emission tomography.

Table 5. List of neurophysiological studies that investigated the prodromal phase.

Year, reference	Design	Sample size (n)	Methods	Definition of the preictal/ premonitory phase	Premonitory symptoms	Provocative	Main findings in the preictal phase
2008, Sand et al. (84)	Longitudinal study (one recording on 3 different days)	– MwoA + MwA, n = 41 (33/8) (13 preattack recordings) – HC, n = 31	VEP	Time criterion: <72 h before headache onset	Not reported	Spontaneous attacks	Increased P1N2 amplitude
2009, Sand et al. (85)	Longitudinal study (one recording on 3 different days)	– MwoA + MwA, n = 41 (33/8) (13 preictal recordings) – HC, n = 31	VEP	Time criterion: <72 h before headache onset	Not reported	Spontaneous attacks	Increased P1N2 amplitude for large checks (62').
2009, Bjørk et al. (93)	Longitudinal study (one recording on 3 different days)	– MwoA + MwA, n = 41 (33/8) (12 preictal recordings)	QEEG	Time criterion: <36 h before headache onset	Not reported	Spontaneous attacks	Increased cortical frontocentral δ activity and posterior α asymmetry
2011, Bjørk et al. (92)	Longitudinal study (one recording on 3 different days)	– MwoA + MwA, n = 41 (33/8) -HC, n = 32	– QEEG frequency spectra – SSVEP	Time criterion: >36 h and <72 h before headache onset	Not reported	Spontaneous attacks	Slowing EEG and asymmetric activity developed
2014, Cosentino et al. (80)	Prospective longitudinal clinical trial	-MwoA + MwA + CM, n = 148 (66, 48, 14) -HC, n = 20	rTMS	Time criterion: <48 h before headache onset	Not reported	Spontaneous attacks	Facilitatory MEP response
2018, McKendrick et al. (86)	Prospective clinical study	– MwoA + MwA, n = 18 – HC, n = 16	-Luminance increment detection in spatial luminance noise – Center surround contrast suppression	Time criterion: no clear definition	Not reported	Spontaneous attacks	Weakened center surround suppression (higher perceived contrast)
2019, Alaydin et al. (83)	Prospective clinical study	– MwoA, n = 25 (5 preictal recordings) – HC, n = 16	TMS (SAI)	Time criterion: <72 h after the procedure	Not reported	Spontaneous attacks	Pronounced decrease in SAI
2019, Mykland et al. (82)	Controlled longitudinal clinical trial (one recording on 3 different days)	– MwoA + MwA, n = 41 (6/41) (11 preictal recordings) – HC, n = 31	EEG recordings when performing one motor and one sensorimotor task	Time criterion: <36 h before headache onset	Not reported	Spontaneous attacks	Increased beta-ERD responses and higher baseline beta power in contralateral sensorimotor cortex for sensorimotor- and motor-tasks
2019, Strupf et al. (91)	Prospective clinical study	– MwoA + MwA, n = 21 (14 /7) – TTH, n = 7 – HC, n = 33	– Pressure and electrical pain – Electrically induced axon-reflex erythema	Time criterion: <26 h before headache onset	Reported	Spontaneous attacks	Reduced habituation of pain perception
2020, Perenboom et al. (94)		– MwoA, n = 20	EEG responses to short	Time criterion:	Not reported		Pre-ictal increase in the

(continued)

Table 5. (continued)

Year, reference	Design	Sample size (n)	Methods	Definition of the preictal/ premonitory phase	Premonitory symptoms	Provocative	Main findings in the preictal phase
	Prospective clinical study	– MwA, n = 19 – HC, n = 24	series of visual flash stimulation over a broad frequency range (chirp stimulation, 10–40 Hz)	<48 h before headache onset		Spontaneous attacks	harmonic EEG response in the beta band
2020, Martins et al. (95)	Prospective observational two-week longitudinal study (daily recordings	– MwoA + MwA, n = 24	Standard EEG spectral analysis and ERP	Time criterion: <24 h before headache onset (data from 24–48 h before the attack was discarded from the analysis)	Reported	Spontaneous attacks	24 h before attack onset: – decrease of relative power in the delta band and increase in beta band at rest – reduction of the amplitude and inter-trial coherence measures of P300
2022, Helfenstein et al. (90)	Prospective longitudinal study (5 consecutive days)	– MwoA + MwA, n = 14 (7/7) – HC, n = 20	– Perception of nociceptive stimuli – Perception of non-nociceptive stimuli – Electrically induced axon-reflex-erythema – Intensity and hedonic estimates of odours	Time criterion: <24 h before headache onset	Reported	Spontaneous attacks	Reduced habituation after five seconds of stimulation at the head
2022, Hsiao et al. (76)	Longitudinal study (30 consecutive days)	– MwoA, n = 2 (3 migraine cycles for each patient)	EEG recording of event-related potentials with the somatosensory and paired pulse paradigms	Time criterion: <24 h before headache onset	Reported	Spontaneous attacks	Somatosensory excitability in the brainstem and primary somatosensory cortex reached its maximum within 24 hours before headache onset

Abbreviations: CM = chronic migraine; EEG = electroencephalogram; ERD = event related desynchronization; ERP = event related potential; h = hours; HC = healthy control; MEP = motor evoked potential; MwA = migraine with aura; MwoA = migraine without aura; PT = pain threshold; QEEG = quantitative electroencephalogram; rTMS = repetitive transcranial magnetic stimulation; SAI = short-latency afferent inhibition; SSVEP = steady-state visual-evoked potential; TMS = transcranial magnetic stimulation; VEP = visual evoked potential.

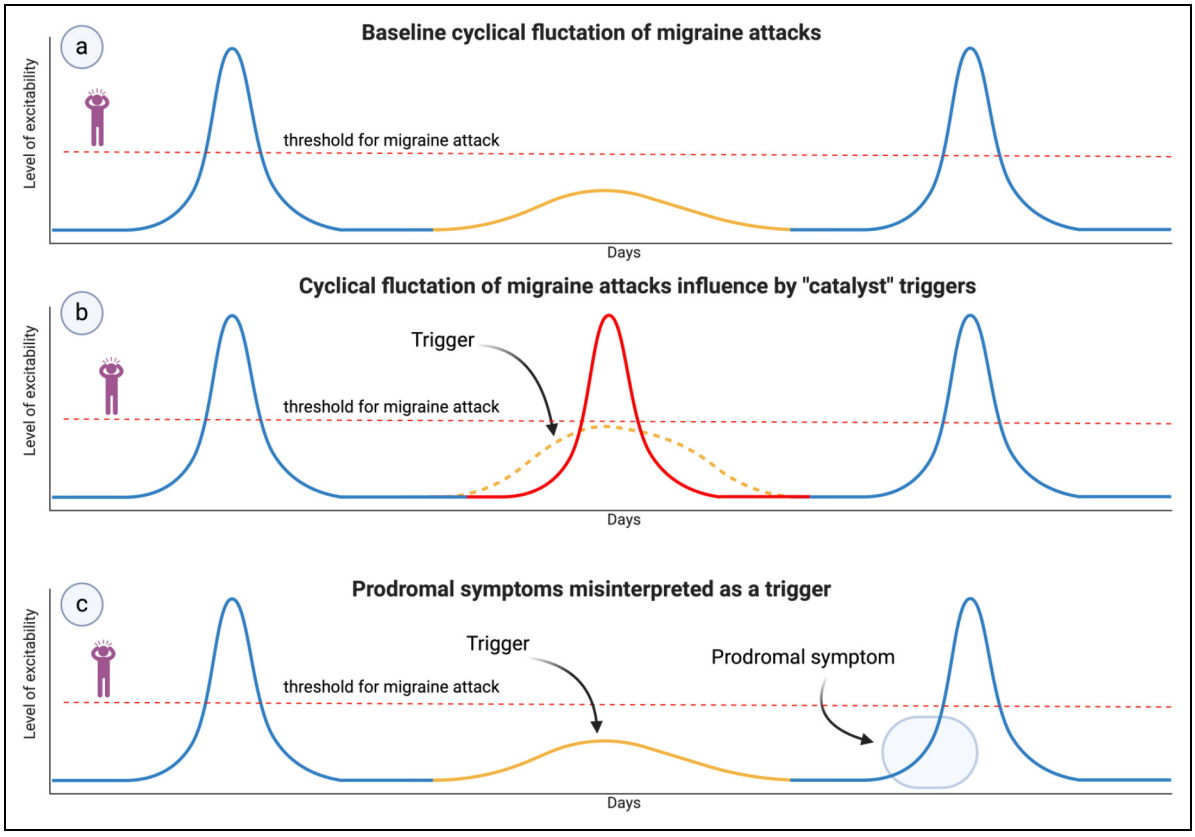

Figure 4. (a) Baseline cyclical fluctuation of cortical excitability. The ictal phase begins when a certain threshold (red dashed line) is overcome. (b) Certain triggers ("catalyst triggers") can facilitate the onset of the migraine attack by acting on cortical excitability and triggering the migraine phase if the patient is close to the migraine threshold. (c) If the patient is far from the threshold of a migraine attack, exposure to the trigger fails to provoke the headache phase. However, prodromal symptoms may arise during some attacks and may be misinterpreted by the patients as a trigger rather than the onset of their migraine attack. Created with BioRender.com.

Certain migraine triggers, such as stress, hormone changes, fasting or sleep deprivation, might play the role of a catalyst by increasing the likelihood of a migraine attack, speeding up the already ongoing modifications of the brain networks. Then, these triggers may influence cortical excitability by activating the hypothalamus (63) or increasing the sensitization of the trigeminal system (120) and can provoke the system to exceed the threshold, leading to attack generation (138). It is plausible that these "catalyst" triggers may facilitate a migraine attack only if the patient is close to the migraine threshold (Figure 4(b)). This could explain the high heterogeneity found in clinical studies because it depends on the specific timing of the migraine cycle during which the patients are being studied. This hypothesis is further justified by the evidence that galcanezumab, a peripherally acting CGRP-monoclonal antibody, was able to reduce the incidence of both PSs and triggers that were followed by headaches in responders with at least 30% migraine frequency reduction (154). Then, reducing pain signaling may restore the normal excitability of several brain areas, including those that mediate PSs (154).

By contrast, external triggers may be less potent with respect to increasing the chance of the upcoming migraine attack. These include some triggers such as exercise and alcohol, which are less commonly reported as migraine triggers (6) and for which the actions may depend on the dose and the system's state, requiring multiple hits to cause the migraine attack.

For other types of external triggers that could be defined as "perceived triggers", such as bright lights, sound or odors, it cannot be excluded that they are PSs misinterpreted as triggers (7,27,53) because they are likely the consequence of activation of certain brain areas during the prodromal phase (Figure 4(c)). However, longitudinal and standardized studies are needed to address this overlap and understand their real pathophysiology.

Importance of understanding the migraine attack onset

Recognizing the difference between prodrome and triggers and distinguishing between true and false triggers is

essential for patients and clinicians. By identifying true triggers, patients can avoid them and reduce certain habits of unmotivated avoidance. Understanding triggers and prodrome would also benefit clinicians and researchers, providing valuable insights into the chronobiology of migraine pathophysiology. Similarly, accurately identifying PSs would allow early treatment of migraine attacks, reducing their disability. Indeed, ubrogepant has shown effectiveness in treating migraine attacks and reducing functional disability when taken during the prodromal phase (155). In this randomized control trial, it was shown that 46% of the qualifying prodrome events were not followed by headache when treated with ubrogepant compared to 29% of those treated with a placebo. Additionally, treatments targeting the CGRP pathway have been confirmed to reduce the frequency of PSs when these drugs are used as preventive treatment (154).

Developing new drugs targeting the central structures implicated in the PSs, such as the hypothalamus or its effector pathways, could improve migraine management.

However, some crucial aspects still need to be fully addressed. In recent years, various systems have been used to track migraine symptoms in a clinical setting: smartphone apps, digital spreadsheets and written migraine diaries. PSs assessment is subject to bias, and proper interpretation of the symptoms reported by the patients is a challenge. Although neurophysiological tests such as electroencephalography, visual evoked potentials, visual processing and quantitative sensory testing could be valuable indicators of different migraine phases, they have limited applicability in daily life (10). A proof of concept study developed an easy-to-use wearable EEG system that recognizes early changes before the migraine attack starts, enabling valuable pre-pain prediction and earlier intervention (95). In this line, the progress of personalized medicine and artificial intelligence will facilitate attack prediction and treatment in the initial phase. Finally, increasing research interest in PSs using triggering models, functional magnetic resonance imaging (fMRI) and randomized controlled trials may be a path to detect new therapeutic targets. Then, by expanding the migraine understanding, we could implement migraine care.

Conclusions

Brain activity and network connectivity changes occur during the prodromal phase. They may result in the development of PSs, which could be misunderstood as triggers. However, the excitatory activity tends to increase during this phase, and certain triggers ("catalyst triggers") might facilitate the onset of the migraine attack by acting on cortical excitability. If the patient is far from the threshold of a migraine attack, exposure to these same triggers is less likely to facilitate the progression to a migraine attack. However, further studies are necessary to test this unifying hypothesis. Understanding triggers and prodromes opens up the possibility of more appropriate and precise migraine care.

Clinical implications

- Migraine triggers and prodromal symptoms can be confused and have an intertwined relationship with the hypothalamus as the central hub for integrating external and internal body signals.
- The prodromal phase is characterized by increased excitability and changes in connectivity within interconnected brain networks. This hyperexcitatory state can be hypothesized as the common link between triggers and prodromal symptoms.
- Certain migraine triggers might increase the likelihood of a migraine attack playing the role of a catalyst in the process of migraine attack generation, whereas others may be falsely interpreted as triggers at the same time as representing the early manifestation of the beginning of the attack.
- Differentiating migraine triggers and prodromal symptoms is crucial to shed light on migraine pathophysiology and improve migraine management.

Acknowledgments

We thank the International Headache Society (IHS) board for organizing the International Headache Academy of the International Headache Society (IHS-iHEAD) working group.

Author contributions

GS, EC and PPR made substantial contributions to the conception, design and revised the work. GS and EC supervised the main working groups. The rest of the authors drafted the work. All authors approved the final version of the manuscript submitted for publication.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: GS received personal fees from AbbVie. KHK received travel grant from AbbVie and honoraria for participation in advisory board from Medison Pharma. MF received personal fees from Novartis and Teva. AÇA, IC, FF, HK, MK, DO, DAM, AP, DS and JS declared no conflict of interest. EC has received honoraria from Novartis, Chiesi, Lundbeck, TEVA, Lilly, Medscape. PPR reports that within the prior 36 months, having received honoraria as a consultant and speaker for: AbbVie, Amgen, Biohaven, Chiesi, Eli Lilly, Lundbeck,

Medscape, Novartis, Pfizer and Teva. Her research group has received research grants from Novartis, Teva, AbbVie, EraNET Neuron, RIS3CAT FEDER, AGAUR, ISCIII and International Headache Society, and has received funding for clinical trials from Alder, Amgen, Biohaven, Eli Lilly, Lundbeck, Novartis and Teva. She is the Honorary Secretary of the International Headache Society. She is a member of the Clinical Trials Guideline Committee of the International Headache Society. She serves as an associate editor for *Cephalalgia*, *Headache*, *The Journal of Headache and Pain*, *Neurologia* and *Revista de Neurologia*. She is the founder of www.midolordecabeza.org. PP-R does not own stocks from any pharmaceutical company.

Funding

The authors received no financial support for the research, authorship and/or publication of this article.

ORCID iDs

Gabriele Sebastianelli https://orcid.org/0000-0002-4231-4417
Kadri-Hebo Kukumägi https://orcid.org/0009-0009-6937-5533
Danilo Antonio Montisano https://orcid.org/0000-0003-4834-2045
Aleksandar Pantovic https://orcid.org/0000-0003-4062-8962
Dmytro Sotnikov https://orcid.org/0000-0001-8030-0369
Edoardo Caronna https://orcid.org/0000-0001-5525-0267
Patricia Pozo-Rosich https://orcid.org/0000-0003-0796-4702

References

1. Goadsby PJ, Holland PR, Martins-Oliveira M, et al. Pathophysiology of migraine: a disorder of sensory processing. *Physiol Rev* 2017; 97: 553–622.
2. Dodick DW. A phase-by-phase review of migraine pathophysiology. *Headache* 2018; 58(Suppl 1): 4–16.
3. Karsan N and Goadsby PJ. Biological insights from the premonitory symptoms of migraine. *Nat Rev Neurol* 2018; 14: 699–710.
4. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. *Cephalalgia* 2018; 38: 1–211.
5. Schulte LH and Peng KP. Current understanding of premonitory networks in migraine: a window to attack generation. *Cephalalgia* 2019; 39: 1720–1727.
6. Kelman L. The triggers or precipitants of the acute migraine attack. *Cephalalgia* 2007; 27: 394–402.
7. Schulte LH, Jürgens TP and May A. Photo-, osmo- and phonophobia in the premonitory phase of migraine: mistaking symptoms for triggers? *J Headache Pain [Internet]*. 2015 [cited 2024 Jan 22]; 16. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4385011/
8. Fischer-Schulte LH and Peng KP. Migraine prodromes and migraine triggers. *Handb Clin Neurol* 2023; 198: 135–148.
9. Pellegrino ABW, Davis-Martin RE, Houle TT, et al. Perceived triggers of primary headache disorders: a meta-analysis. *Cephalalgia* 2018; 38: 1188–1198.
10. Peng KP and May A. Redefining migraine phases – a suggestion based on clinical, physiological, and functional imaging evidence. *Cephalalgia* 2020; 40: 866–870.
11. Cao Z, Lai KL, Lin CT, et al. Exploring resting-state EEG complexity before migraine attacks. *Cephalalgia* 2018; 38: 1296–1306.
12. Giffin NJ, Ruggiero L, Lipton RB, et al. Premonitory symptoms in migraine: an electronic diary study. *Neurology* 2003; 60: 935–940.
13. Karsan N, Bose P and Goadsby PJ. The migraine premonitory phase. *Contin Minneap Minn* 2018; 24: 996–1008.
14. Holsteen KK, Hittle M, Barad M, et al. Development and internal validation of a multivariable prediction model for individual episodic migraine attacks based on daily trigger exposures. *Headache* 2020; 60: 2364–2379.
15. Gago-Veiga AB, Pagán J, Henares K, et al. To what extent are patients with migraine able to predict attacks? *J Pain Res* 2018; 11: 2083–2094.
16. Do TP, Hougaard A, Dussor G, et al. Migraine attacks are of peripheral origin: the debate goes on. *J Headache Pain* 2023; 24: 3.
17. Karli N, Zarifoglu M, Calisir N, et al. Comparison of preheadache phases and trigger factors of migraine and episodic tension-type headache: do they share similar clinical pathophysiology? *Cephalalgia* 2005; 25: 444–451.
18. Schoonman GG, Evers DJ, Terwindt GM, et al. The prevalence of premonitory symptoms in migraine: a questionnaire study in 461 patients. *Cephalalgia* 2006; 26: 1209–1213.
19. Quintela E, Castillo J, Muñoz P, et al. Premonitory and resolution symptoms in migraine: a prospective study in 100 unselected patients. *Cephalalgia* 2006; 26: 1051–1060.
20. Karsan N, Bose P, Newman J, et al. Are some patient-perceived migraine triggers simply early manifestations of the attack? *J Neurol* 2021; 268: 1885–1893.
21. Ran Y, Yin Z, Lian Y, et al. Gradually shifting clinical phenomics in migraine spectrum: a cross-sectional, multicenter study of 5438 patients. *J Headache Pain* 2022; 23: 89.
22. Thuraiaiyah J, Ashina H, Christensen RH, et al. Premonitory symptoms in migraine: a REFORM study. *Cephalalgia* 2024; 44: 03331024231223979.
23. Güven B, Güven H and Çomoğlu SS. Migraine and yawning. *Headache* 2018; 58: 210–216.
24. Kelman L. The premonitory symptoms (prodrome): a tertiary care study of 893 migraineurs. *Headache* 2004; 44: 865–872.
25. Laurell K, Artto V, Bendtsen L, et al. Premonitory symptoms in migraine: a cross-sectional study in 2714 persons. *Cephalalgia* 2016; 36: 951–959.
26. Schwedt TJ, Peplinski J, Garcia-Filion P, et al. Altered speech with migraine attacks: a prospective, longitudinal study of episodic migraine without aura. *Cephalalgia* 2019; 39: 722–731.
27. Wang X, Yin Z, Lian Y, et al. Premonitory symptoms in migraine from China: a multi-clinic study of 4821 patients. *Cephalalgia* 2021; 41: 991–1003.
28. Pradhan S and Choudhury SS. Clinical characterization of neck pain in migraine. *Neurol India* 2018; 66: 377–384.
29. Turner DP and Houle TT. Influences on headache trigger beliefs and perceptions. *Cephalalgia* 2018; 38: 1545–1553.
30. Xie YJ, Lin M, Wong YT, et al. Migraine attacks and relevant trigger factors in undergraduate nursing students in

Hong Kong: a cross-sectional study. *J Pain Res* 2022; 15: 701–713.
31. Gu X and Xie Y. Migraine attacks among medical students in soochow university, southeast China: a cross-sectional study. *J Pain Res* 2018; 11: 771–781.
32. Aljaafari D, Aldossary N, Almuaigel MF, et al. Migraine prevalence, characteristics, triggers, and coping strategies among medical students in Saudi Arabia. *Prim Care Companion CNS Disord* 2021; 23: 20m02859.
33. Turner DP, Lebowitz AD, Chtay I, et al. Headache triggers as surprise. *Headache* 2019; 59: 495–508.
34. Al-Hashel JY, Ahmed SF, Alroughani R, et al. Migraine among medical students in Kuwait university. *J Headache Pain* 2014; 15: 26.
35. Athar F, Zahid A, Farooq M, et al. Frequency of migraine according to the ICHD-3 criteria and its association with sociodemographic and triggering factors in Pakistan: a cross-sectional study. *Ann Med Surg 2012* 2022; 82: 104589.
36. Chądzyński P, Kacprzak A, Domitrz W, et al. Migraine headache facilitators in a population of Polish women and their association with migraine occurrence – preliminary results. *Neurol Neurochir Pol* 2019; 53: 377–383.
37. Iliopoulos P, Damigos D, Kerezoudi E, et al. Trigger factors in primary headaches subtypes: a cross-sectional study from a tertiary centre in Greece. *BMC Res Notes* 2015; 8: 393.
38. Park JW, Chu MK, Kim JM, et al. Analysis of trigger factors in episodic migraineurs using a smartphone headache diary applications. *PloS One* 2016; 11: e0149577.
39. Anaya F, Abu Alia W, Hamoudeh F, et al. Epidemiological and clinical characteristics of headache among medical students in palestine: a cross sectional study. *BMC Neurol* 2022; 22: 4.
40. Constantinides V, Anagnostou E, Bougea A, et al. Migraine and tension-type headache triggers in a Greek population. *Arq Neuropsiquiatr* 2015; 73: 665–669.
41. Mostofsky E, Bertisch SM, Vgontzas A, et al. Prospective cohort study of daily alcoholic beverage intake as a potential trigger of headaches among adults with episodic migraine. *Ann Med* 2020; 52: 386–392.
42. Onderwater GLJ, van Oosterhout WPJ, Schoonman GG, et al. Alcoholic beverages as trigger factor and the effect on alcohol consumption behavior in patients with migraine. *Eur J Neurol* 2019; 26: 588–595.
43. Spierings EL, Ranke AH and Honkoop PC. Precipitating and aggravating factors of migraine versus tension-type headache. *Headache* 2001; 41: 554–558.
44. Zivadinov R, Willheim K, Sepic-Grahovac D, et al. Migraine and tension-type headache in Croatia: a population-based survey of precipitating factors. *Cephalalgia* 2003; 23: 336–343.
45. Wöber C, Holzhammer J, Zeitlhofer J, et al. Trigger factors of migraine and tension-type headache: experience and knowledge of the patients. *J Headache Pain* 2006; 7: 188–195.
46. Hauge AW, Kirchmann M and Olesen J. Characterization of consistent triggers of migraine with aura. *Cephalalgia* 2011; 31: 416–438.
47. Mollaoğlu M. Trigger factors in migraine patients. *J Health Psychol* 2013; 18: 984–994.
48. Lampl C, Rudolph M, Deligianni CI, et al. Neck pain in episodic migraine: premonitory symptom or part of the attack? *J Headache Pain* 2015; 16: 566.
49. Eigenbrodt AK, Christensen RH, Ashina H, et al. Premonitory symptoms in migraine: a systematic review and meta-analysis of observational studies reporting prevalence or relative frequency. *J Headache Pain* 2022; 23: 140.
50. Becker WJ. The premonitory phase of migraine and migraine management. *Cephalalgia* 2013; 33: 1117–1121.
51. Lipton RB, Lanteri-Minet M, Leroux E, et al. Pre- and post-headache phases of migraine: multi-country results from the CaMEO – international study. *J Headache Pain* 2023; 24: 151.
52. Marmura MJ. Triggers, protectors, and predictors in episodic migraine. *Curr Pain Headache Rep* 2018; 22: 81.
53. Pavlovic JM, Buse DC, Sollars CM, et al. Trigger factors and premonitory features of migraine attacks: summary of studies. *Headache* 2014; 54: 1670–1679.
54. Lipton RB, Pavlovic JM, Haut SR, et al. Methodological issues in studying trigger factors and premonitory features of migraine. *Headache* 2014; 54: 1661–1669.
55. Casanova A, Vives-Mestres M, Donoghue S, et al. An observational study of self-reported migraine triggers and prospective evaluation of the relationships with occurrence of attacks enabled by a smartphone application (app). *Headache* 2022; 62: 1406–1415.
56. Casanova A, Vives-Mestres M, Donoghue S, et al. The role of avoiding known triggers, embracing protectors, and adhering to healthy lifestyle recommendations in migraine prophylaxis: insights from a prospective cohort of 1125 people with episodic migraine. *Headache* 2023; 63: 51–61.
57. Ashina M, Hansen JM, Do TP, et al. Migraine and the trigeminovascular system-40 years and counting. *Lancet Neurol* 2019; 18: 795–804.
58. Blau JN. Migraine prodromes separated from the aura: complete migraine. *Br Med J* 1980; 281: 658–660.
59. Schulte LH and May A. The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. *Brain J Neurol* 2016; 139(Pt 7): 1987–1993.
60. Maniyar FH, Sprenger T, Monteith T, et al. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. *Brain J Neurol* 2014; 137(Pt 1): 232–241.
61. Mehnert J, Fischer-Schulte L and May A. Aura phenomena do not initiate migraine attacks-findings from neuroimaging. *Headache* 2023; 63: 1040–1044.
62. Schulte LH, Mehnert J and May A. Longitudinal neuroimaging over 30 days: temporal characteristics of migraine. *Ann Neurol* 2020; 87: 646–651.
63. Noseda R, Kainz V, Borsook D, et al. Neurochemical pathways that converge on thalamic trigeminovascular neurons: potential substrate for modulation of migraine by sleep, food intake, stress and anxiety. *PLOS ONE* 2014; 9: e103929.
64. Al-Khazali HM, Krøll LS, Ashina H, et al. Neck pain and headache: pathophysiology, treatments and future directions. *Musculoskelet Sci Pract* 2023; 66: 102804.
65. Maniyar FH, Sprenger T, Schankin C, et al. The origin of nausea in migraine-a PET study. *J Headache Pain* 2014; 15: 84.
66. Kannan H and Yamashita H. Connections of neurons in the region of the nucleus tractus solitarius with the hypothalamic

paraventricular nucleus: their possible involvement in neural control of the cardiovascular system in rats. *Brain Res* 1985; 329: 205–212.
67. Kaube H, Keay KA, Hoskin KL, et al. Expression of c-fos-like immunoreactivity in the caudal medulla and upper cervical spinal cord following stimulation of the superior sagittal sinus in the cat. *Brain Res* 1993; 629: 95–102.
68. Karsan N, Bose RP, O'Daly O, et al. Regional cerebral perfusion during the premonitory phase of triggered migraine: a double-blind randomized placebo-controlled functional imaging study using pseudo-continuous arterial spin labeling. *Headache* 2023; 63: 771–787.
69. Maniyar FH, Sprenger T, Schankin C, et al. Photic hypersensitivity in the premonitory phase of migraine–a positron emission tomography study. *Eur J Neurol* 2014; 21: 1178–1183.
70. Noseda R, Jakubowski M, Kainz V, et al. Cortical projections of functionally identified thalamic trigeminovascular neurons: implications for migraine headache and its associated symptoms. *J Neurosci* 2011; 31: 14204–14217.
71. Noseda R, Kainz V, Jakubowski M, et al. A neural mechanism for exacerbation of headache by light. *Nat Neurosci* 2010; 13: 239–245.
72. Kagan R, Kainz V, Burstein R, et al. Hypothalamic and basal ganglia projections to the posterior thalamus: possible role in modulation of migraine headache and photophobia. *Neuroscience* 2013; 248: 359–368.
73. Karsan N, Bose PR, O'Daly O, et al. Alterations in functional connectivity during different phases of the triggered migraine attack. *Headache* 2020; 60: 1244–1258.
74. Schulte LH, Menz MM, Haaker J, et al. The migraineur's brain networks: continuous resting state fMRI over 30 days. *Cephalalgia* 2020; 40: 1614–1621.
75. Meylakh N, Marciszewski KK, Di Pietro F, et al. Brainstem functional oscillations across the migraine cycle: a longitudinal investigation. *NeuroImage Clin* 2021; 30: 102630.
76. Hsiao FJ, Chen WT, Pan LLH, et al. Dynamic brainstem and somatosensory cortical excitability during migraine cycles. *J Headache Pain* 2022; 23: 21.
77. Coppola G, Tinelli E, Lepre C, et al. Dynamic changes in thalamic microstructure of migraine without aura patients: a diffusion tensor magnetic resonance imaging study. *Eur J Neurol* 2014; 21: 287–e13.
78. Martinelli D, Castellazzi G, De Icco R, et al. Thalamocortical connectivity in experimentally-induced migraine attacks: a pilot study. *Brain Sci* 2021; 11: 165.
79. Stankewitz A, Keidel L, Rehm M, et al. Migraine attacks as a result of hypothalamic loss of control. *NeuroImage Clin* 2021; 32: 102784.
80. Cosentino G, Fierro B, Vigneri S, et al. Cyclical changes of cortical excitability and metaplasticity in migraine: evidence from a repetitive transcranial magnetic stimulation study. *Pain* 2014; 155: 1070–1078.
81. Coppola G, Bracaglia M, Di Lenola D, et al. Lateral inhibition in the somatosensory cortex during and between migraine without aura attacks: correlations with thalamocortical activity and clinical features. *Cephalalgia* 2016; 36: 568–578.
82. Mykland MS, Bjørk MH, Stjern M, et al. Fluctuations of sensorimotor processing in migraine: a controlled longitudinal study of beta event related desynchronization. *J Headache Pain* 2019; 20: 77.
83. Alaydin HC, Vuralli D, Keceli Y, et al. Reduced short-latency afferent inhibition indicates impaired sensorimotor integrity during migraine attacks. *Headache* 2019; 59: 906–914.
84. Sand T, Zhitniy N, White LR, et al. Visual evoked potential latency, amplitude and habituation in migraine: a longitudinal study. *Clin Neurophysiol* 2008; 119: 1020–1027.
85. Sand T, White LR, Hagen K, et al. Visual evoked potential and spatial frequency in migraine: a longitudinal study. *Acta Neurol Scand Suppl* 2009; 189: 33–37.
86. McKendrick AM, Chan YM, Vingrys AJ, et al. Daily vision testing can expose the prodromal phase of migraine. *Cephalalgia* 2018; 38: 1575–1584.
87. Ikumi N, Marti-Marca A, de la Torre-Suñe A, et al. Quantifying sensory thresholds along the migraine cycle: an exploratory longitudinal study. *Cephalalgia* 2024; 44: 3331024241230279.
88. Uglem M, Omland PM, Nilsen KB, et al. Does pain sensitivity change by migraine phase? A blinded longitudinal study. *Cephalalgia* 2017; 37: 1337–1349.
89. Marti-Marca A, Vilà-Balló A, Cerda-Company X, et al. Exploring sensory sensitivity, cortical excitability, and habituation in episodic migraine, as a function of age and disease severity, using the pattern-reversal task. *J Headache Pain* 2023; 24: 104.
90. Helfenstein C, Strupf M, Stefke A, et al. Cyclic changes of sensory parameters in migraine patients. *Cephalalgia* 2022; 42: 1148–1159.
91. Strupf M, Fraunberger B, Messlinger K, et al. Cyclic changes in sensations to painful stimuli in migraine patients. *Cephalalgia* 2019; 39: 585–596.
92. Bjørk M, Stovner LJ, Hagen K, et al. What initiates a migraine attack? Conclusions from four longitudinal studies of quantitative EEG and steady-state visual-evoked potentials in migraineurs. *Acta Neurol Scand Suppl* 2011; 191: 56–63.
93. Bjørk MH, Stovner LJ, Engstrøm M, et al. Interictal quantitative EEG in migraine: a blinded controlled study. *J Headache Pain* 2009; 10: 331–339.
94. Perenboom MJ, van de Ruit M, Zielman R, et al. Enhanced pre-ictal cortical responsivity in migraine patients assessed by visual chirp stimulation. *Cephalalgia* 2020; 40: 913–923.
95. Martins IP, Westerfield M, Lopes M, et al. Brain state monitoring for the future prediction of migraine attacks. *Cephalalgia* 2020; 40: 255–265.
96. Meylakh N, Marciszewski KK, Di Pietro F, et al. Deep in the brain: changes in subcortical function immediately preceding a migraine attack. *Hum Brain Mapp* 2018; 39: 2651–2663.
97. Ashina M, Hansen JM, á Dunga BO, et al. Human models of migraine—short-term pain for long-term gain. *Nat Rev Neurol* 2017; 13: 713–724.
98. Broessner G, Rohregger J, Wille M, et al. Hypoxia triggers high-altitude headache with migraine features: a prospective trial. *Cephalalgia* 2016; 36: 765–771.
99. Schoonman GG, Sándor PS, Agosti RM, et al. Normobaric hypoxia and nitroglycerin as trigger factors for migraine. *Cephalalgia* 2006; 26: 816–819.

100. Afridi KS, Kaube H and Goadsby JP. Glyceryl trinitrate triggers premonitory symptoms in migraineurs. *Pain* 2004; 110: 675–680.
101. Guo S, Vollesen ALH, Olesen J, et al. Premonitory and non-headache symptoms induced by CGRP and PACAP38 in patients with migraine. *Pain* 2016; 157: 2773–2781.
102. Karsan N, Bose PR, Thompson C, et al. Headache and non-headache symptoms provoked by nitroglycerin in migraineurs: a human pharmacological triggering study. *Cephalalgia* 2020; 40: 828–841.
103. Craig AD. Interoception: the sense of the physiological condition of the body. *Curr Opin Neurobiol* 2003; 13: 500–505.
104. Borsook D, Veggeberg R, Erpelding N, et al. The Insula: a 'hub of activity' in migraine. *Neurosci Rev J Bringing Neurobiol Neurol Psychiatry* 2016; 22: 632–652.
105. Sedley W, Kumar S, Jones S, et al. Migraine as an allostatic reset triggered by unresolved interoceptive prediction errors. *Neurosci Biobehav Rev* 2024; 157: 105536.
106. Zhang X, Levy D, Noseda R, et al. Activation of meningeal nociceptors by cortical spreading depression: implications for migraine with aura. *J Neurosci* 2010; 30: 8807–8814.
107. Bolay H, Reuter U, Dunn AK, et al. Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. *Nat Med* 2002; 8: 136–142.
108. Moskowitz MA, Nozaki K and Kraig RP. Neocortical spreading depression provokes the expression of c-fos protein-like immunoreactivity within trigeminal nucleus caudalis via trigeminovascular mechanisms. *J Neurosci* 1993; 13: 1167–1177.
109. Joëls M, Karst H and Sarabdjitsingh RA. The stressed brain of humans and rodents. *Acta Physiol Oxf Engl* 2018; 223: e13066.
110. Shyti R, Eikermann-Haerter K, van Heiningen SH, et al. Stress hormone corticosterone enhances susceptibility to cortical spreading depression in familial hemiplegic migraine type 1 mutant mice. *Exp Neurol* 2015; 263: 214–220.
111. Kaufmann D and Brennan KC. The effects of chronic stress on migraine relevant phenotypes in male mice. *Front Cell Neurosci* 2018; 12: 294.
112. Balkaya M, Seidel JL, Sadeghian H, et al. Relief following chronic stress augments spreading depolarization susceptibility in familial hemiplegic migraine mice. *Neuroscience* 2019; 415: 1–9.
113. Yapıcı-Eser H, Dönmez-Demir B, Kılıç K, et al. Stress modulates cortical excitability via α-2 adrenergic and glucocorticoid receptors: as assessed by spreading depression. *Exp Neurol* 2018; 307: 45–51.
114. Lipton RB, Buse DC, Hall CB, et al. Reduction in perceived stress as a migraine trigger. *Neurology* 2014; 82: 1395–1401.
115. Eikermann-Haerter K, Dileköz E, Kudo C, et al. Genetic and hormonal factors modulate spreading depression and transient hemiparesis in mouse models of familial hemiplegic migraine type 1. *J Clin Invest* 2009; 119: 99–109.
116. Brennan KC, Romero Reyes M, López Valdés HE, et al. Reduced threshold for cortical spreading depression in female mice. *Ann Neurol* 2007; 61: 603–606.
117. Eikermann-Haerter K, Baum MJ, Ferrari MD, et al. Androgenic suppression of spreading depression in familial hemiplegic migraine type 1 mutant mice. *Ann Neurol* 2009; 66: 564–568.
118. Kudo C, Harriott AM, Moskowitz MA, et al. Estrogen modulation of cortical spreading depression. *J Headache Pain* 2023; 24: 62.
119. Siniatchkin M, Averkina N and Gerber WD. Relationship between precipitating agents and neurophysiological abnormalities in migraine. *Cephalalgia* 2006; 26: 457–465.
120. Martin VT, Lee J and Behbehani MM. Sensitization of the trigeminal sensory system during different stages of the rat estrous cycle: implications for menstrual migraine. *Headache* 2007; 47: 552–563.
121. Raffaelli B, Storch E, Overeem LH, et al. Sex hormones and calcitonin gene-related peptide in women with migraine: a cross-sectional, matched cohort study. *Neurology* 2023; 100: e1825–e1835.
122. Al-Hashel JY, Abokalawa F, Toma R, et al. Worsening of migraine headache with fasting ramadan. *Clin Neurol Neurosurg* 2021; 209: 106899.
123. Ragab AH, Kishk NA, Hassan A, et al. Changes in migraine characteristics over 30 days of ramadan fasting: a prospective study. *Headache* 2021; 61: 1493–1498.
124. Abu-Salameh I, Plakht Y and Ifergane G. Migraine exacerbation during ramadan fasting. *J Headache Pain* 2010; 11: 513–517.
125. Kilic K, Karatas H, Dönmez-Demir B, et al. Inadequate brain glycogen or sleep increases spreading depression susceptibility. *Ann Neurol* 2018; 83: 61–73.
126. Mykland MS, Uglem M, Neverdahl JP, et al. Sleep restriction alters cortical inhibition in migraine: a transcranial magnetic stimulation study. *Clin Neurophysiol* 2022; 139: 28–42.
127. Mykland MS, Uglem M, Stovner LJ, et al. Insufficient sleep may alter cortical excitability near the migraine attack: a blinded TMS crossover study. *Cephalalgia* 2023; 43: 3331024221148391.
128. Panconesi A, Bartolozzi ML, Mugnai S, et al. Alcohol as a dietary trigger of primary headaches: what triggering site could be compatible? *Neurol Sci* 2012; 33(Suppl 1): S203–S205.
129. Panconesi A. Alcohol-induced headaches: evidence for a central mechanism? *J Neurosci Rural Pract* 2016; 7: 269–275.
130. Nicoletti P, Trevisani M, Manconi M, et al. Ethanol causes neurogenic vasodilation by TRPV1 activation and CGRP release in the trigeminovascular system of the Guinea pig. *Cephalalgia* 2008; 28: 9–17.
131. Gundersen H, van Wageningen H and Grüner R. Alcohol-induced changes in cerebral blood flow and cerebral blood volume in social drinkers. *Alcohol Alcohol Oxf Oxfs* 2013; 48: 160–165.
132. Marxen M, Gan G, Schwarz D, et al. Acute effects of alcohol on brain perfusion monitored with arterial spin labeling magnetic resonance imaging in young adults. *J Cereb Blood Flow Metab* 2014; 34: 472–479.
133. de Mora F and Messlinger K. Is calcitonin gene-related peptide (CGRP) the missing link in food histamine-induced migraine? A review of functional gut-to-trigeminovascular system connections. *Drug Discov Today* 2024; 29: 103941.
134. Henderson W and Raskin N. "Hot-Dog" headache: individual susceptibility to nitrite. *The Lancet* 1972; 300: 1162–1163.
135. Silva-Néto RP, Bezerra GL, Araújo NRA, et al. Migraine attacks triggered by ingestion of watermelon. *Eur Neurol* 2023; 86: 250–255.

136. Gibb CM, Davies PT, Glover V, et al. Chocolate is a migraine-provoking agent. *Cephalalgia* 1991; 11: 93–95.
137. Marcus DA, Scharff L, Turk D, et al. A double-blind provocative study of chocolate as a trigger of headache. *Cephalalgia* 1997; 17: 855–862. discussion 800.
138. Lindblad M, Hougaard A, Amin FM, et al. Can migraine aura be provoked experimentally? A systematic review of potential methods for the provocation of migraine aura. *Cephalalgia* 2017; 37: 74–88.
139. Hougaard A, Amin FM, Hauge AW, et al. Provocation of migraine with aura using natural trigger factors. *Neurology* 2013; 80: 428–431.
140. Hanalioglu S, Taskiran-Sag A, Karatas H, et al. Cortical spreading depression can be triggered by sensory stimulation in primed wild type mouse brain: a mechanistic insight to migraine aura generation. *J Headache Pain* 2022; 23: 107.
141. Amin FM, Aristeidou S, Baraldi C, et al. The association between migraine and physical exercise. *J Headache Pain* 2018; 19: 83.
142. Varkey E, Cider A, Carlsson J, et al. Exercise as migraine prophylaxis: a randomized study using relaxation and topiramate as controls. *Cephalalgia* 2011; 31: 1428–1438.
143. Köseoglu E, Akboyraz A, Soyuer A, et al. Aerobic exercise and plasma beta endorphin levels in patients with migrainous headache without aura. *Cephalalgia* 2003; 23: 972–976.
144. Varkey E, Hagen K, Zwart JA, et al. Physical activity and headache: results from the nord-trøndelag health study (HUNT). *Cephalalgia* 2008; 28: 1292–1297.
145. Molarius A, Tegelberg A and Ohrvik J. Socio-economic factors, lifestyle, and headache disorders – a population-based study in Sweden. *Headache* 2008; 48: 1426–1437.
146. Varkey E, Grüner Sveälv B, Edin F, et al. Provocation of migraine after maximal exercise: a test-retest study. *Eur Neurol* 2017; 78: 22–27.
147. Koppen H and van Veldhoven PLJ. Migraineurs with exercise-triggered attacks have a distinct migraine. *J Headache Pain* 2013; 14: 99.
148. Watanabe H, Kuwabara T, Ohkubo M, et al. Elevation of cerebral lactate detected by localized 1H-magnetic resonance spectroscopy in migraine during the interictal period. *Neurology* 1996; 47: 1093–1095.
149. Jonhagen S, Ackermann P, Saartok T, et al. Calcitonin gene related peptide and neuropeptide Y in skeletal muscle after eccentric exercise: a microdialysis study. *Br J Sports Med* 2006; 40: 264–267.
150. Tarperi C, Sanchis-Gomar F, Montagnana M, et al. Effects of endurance exercise on serum concentration of calcitonin gene-related peptide (CGRP): a potential link between exercise intensity and headache. *Clin Chem Lab Med* 2020; 58: 1707–1712.
151. Karsan N and Goadsby PJ. Neuroimaging in the pre-ictal or premonitory phase of migraine: a narrative review. *J Headache Pain* 2023; 24: 106.
152. Peng KP and May A. Migraine understood as a sensory threshold disease. *Pain* 2019; 160: 1494–1501.
153. Noseda R, Borsook D and Burstein R. Neuropeptides and neurotransmitters that modulate thalamo-cortical pathways relevant to migraine headache. *Headache* 2017; 57(S2): 97–111.
154. Ashina S, Melo-Carrillo A, Toluwanimi A, et al. Galcanezumab effects on incidence of headache after occurrence of triggers, premonitory symptoms, and aura in responders, non-responders, super-responders, and super non-responders. *J Headache Pain* 2023; 24: 26.
155. Dodick DW, Goadsby PJ, Schwedt TJ, et al. Ubrogepant for the treatment of migraine attacks during the prodrome: a phase 3, multicentre, randomised, double-blind, placebo-controlled, crossover trial in the USA. *Lancet Lond Engl* 2023; 402: 2307–2316.