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# Premonitory symptoms in glyceryl trinitrate triggered migraine attacks: a case-control study

Gerrit L.J. Onderwater\*, Jitze Dool, Michel D. Ferrari, Gisela M. Terwindt

## Abstract

Spontaneous and pharmacologically provoked migraine attacks are frequently preceded by nonheadache symptoms called premonitory symptoms. Here, we systematically evaluated premonitory symptoms in migraine patients and healthy controls after glyceryl trinitrate (GTN) infusion. In women with migraine without aura ( $n = 34$ ) and age-matched female controls ( $n = 24$ ), we conducted systematically a semistructured interview assessing 21 possible premonitory symptoms every 15 minutes in the 5 hours after GTN infusion ( $0.5 \mu\text{g/kg/min}$  over 20 minutes). Migraine-like headaches occurred in 28/34 (82.4%) migraineurs (GTN responders). After GTN, 26/28 (92.9%) responders, 6/6 (100%) nonresponders, and 13/24 (54.2%) controls reported at least one possible premonitory symptom. Concentration difficulties ( $P = 0.011$ ), yawning ( $P = 0.009$ ), nausea ( $P = 0.028$ ), and photophobia ( $P = 0.001$ ) were more frequently reported by those migraineurs who developed a migraine-like attack vs healthy controls. Importantly, concentration difficulties were exclusively reported by those who developed a migraine-like attack. Thus, our findings support the view that GTN is able to provoke the naturally occurring premonitory symptoms and show that yawning, nausea, photophobia, and concentration difficulties are most specific for an impending GTN-induced migraine-like headache. We suggest that these symptoms may also be helpful as early warning signals in clinical practice with concentration difficulties exclusively reported by those who develop a migraine-like attack.

**Keywords:** Migraine, Glyceryl trinitrate, Premonitory symptoms, Prodromal symptoms

## 1. Introduction

Migraine is a highly prevalent episodic neurovascular brain disorder, causing severe disability worldwide.<sup>15,28,42</sup> In up to 90% of patients, the onset of a migraine attack is characterized by a premonitory phase with accompanying nonheadache symptoms called premonitory symptoms.<sup>24,40,44</sup> Premonitory symptoms are able to precede the migraine headache up to 72 hours<sup>12</sup> and may persist in the subsequent aura (if applicable) and headache phase, even up to the prodromal phase.<sup>11,12,20,24</sup> Some of these nonheadache symptoms as photophobia, phonophobia, nausea, and vomiting are also included as associated symptoms in the criteria for migrainous headache.<sup>21</sup>

Reported premonitory symptoms are numerous and span various categories such as homeostatic alterations, sensory sensitivities, mood, cognitive, and fatigue symptoms, which are regularly mislabelled by patients as triggers.<sup>16,24,25</sup> Frequently reported symptoms include concentration impairment, tiredness/fatigue, food cravings, irritability, yawning, photophobia, and neck stiffness.<sup>7,27,40</sup> Given the nature and often circadian rhythmicity of premonitory symptoms, the hypothalamus with orexinergic (sleep regulation and feeding) and dopaminergic (yawning and nausea) systems has been suggested to be implicated.<sup>16</sup> This is supported by neuroimaging findings showing hypothalamic involvement preceding and during spontaneous<sup>9,41</sup> and pharmacologically triggered migraine(-like) attacks.<sup>30</sup> The presence and endurance of premonitory symptoms into consecutive migraine phases have also been suggested to occur when triggered by pharmacological substances.<sup>17,18</sup> The most well-known migraine provocation model relies on intravenous infusion with the nitric oxide donor glyceryl trinitrate (GTN),<sup>6</sup> and premonitory symptoms have also been reported after GTN infusion,<sup>1,30</sup> with activation of hypothalamic regions preceding the onset of migraine-like headaches.<sup>30</sup>

Premonitory symptoms may go unrecognized by patients unless specifically asked for, due to their limited specificity which is illustrated by the reported prevalence ranging from 7% to 88% of patients.<sup>24,39,44</sup> Common and nonspecific nonheadache symptoms as yawning, food craving, and tiredness/fatigue are likely also experienced on a day-to-day basis by the general population not suffering from migraine.<sup>12</sup> However, because healthy controls logically do not suffer from migraine attacks, no prevalence studies or pharmacological provocation studies systematically and prospectively investigated the onset and specificity of these symptoms in migraine patients compared

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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with healthy volunteers. Pharmacological migraine models provide an opportunity for clinical investigation of symptoms occurring before and during an attack under precisely controlled and regulated conditions<sup>5,6</sup> and allow for detailed prospective monitoring of the presence and timing of symptom onset. Detailed knowledge on premonitory symptoms could offer insights into pathophysiological mechanisms involved in the early phases of a migraine attack.

In this study, we aimed to compare the presence of premonitory symptoms after GTN under matched conditions between age-matched female migraine patients and healthy controls, and between attack responders and nonresponders. Second, we aimed to investigate the timing and persistence of these nonheadache symptoms after GTN administration.

## 2. Methods

### 2.1. Participants

We included 2 age-matched study groups consisting of female migraine without aura patients ( $n = 37$ ) and healthy female controls ( $n = 25$ ). Migraine without aura was diagnosed in accordance with the International Classification of Headache Disorders (ICHD-3).<sup>21</sup> Participants with migraine experienced at least one migraine attack per month during the 6 months before the investigation, did not have chronic migraine or medication-overuse headache, and were otherwise healthy. Healthy female controls were free of any neurological or psychiatric disorders and primary or secondary headaches apart from occasional episodic tension-type headache. Furthermore, healthy controls did not report a first degree family member with migraine or trigeminal autonomic cephalgia. None of the participants used any chronic medication other than possibly oral contraceptives. Participants in this study were part of an imaging study consisting of 3 scan sessions during a single day, aimed at the onset of migraine-like attacks triggered by GTN. Participants were recruited from the Leiden University Medical Center Migraine Neuro Analysis project in which migraineurs and controls from the Dutch population are listed who have agreed to participate in migraine-related scientific research and by public advertisement.<sup>37</sup> The study was approved by the medical ethics committee of the Leiden University Medical Center. All participants provided written informed consent before participation.

### 2.2. Study design

In this longitudinal prospective study, participants arrived at 07:30 AM at the hospital in a nonfasting state. Participants were instructed to abstain from alcoholic beverages, caffeinated beverages, and smoking for at least 8 hours before the first scan session and were allowed to eat during the course of the day. Migraineurs did not use any prophylactic medication for at least 4 weeks and were at least 3 days attack-free before the investigation. At the hospital, participants were interviewed and underwent a neurological examination before undergoing 3 magnetic resonance imaging scans. The interview included questions regarding migraine and headache frequency, presence of headache, and 21 premonitory symptoms. Between 9:45 and 10:45 AM, GTN (0.5  $\mu\text{g}/\text{kg}/\text{min}$  over 20 minutes) was administered by intravenous infusion with the participant in supine position. Participants were informed GTN could potentially induce headache but were not informed of the timing or characteristics of the headache. Five minutes before the start of the GTN infusion, the presence of possible premonitory symptoms, headache, and associated symptoms was registered. During the actual GTN

infusion (20 minutes), headache and associated symptoms were documented every 5 minutes. After this infusion period, the occurrence of premonitory symptoms, headache, and associated symptoms were documented every 15 minutes until 5 hours after GTN infusion, except for the time around MR scanning (directly before MR scanning [only headache and associated symptoms] and during MR scanning [no questionnaire]). After the study day, participants were asked to fill in a headache diary at home for 7 days after the study day (participants with migraine also filled in a headache diary 7 days before the study day).

### 2.3. Premonitory symptoms and migraine-like attacks

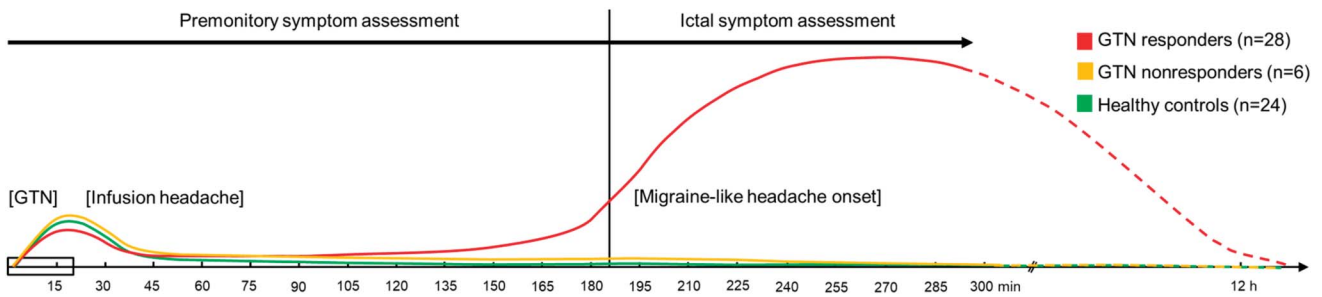
The ICHD-3 defines premonitory symptoms as symptoms warning of a migraine attack and occurring 48 hours before onset.<sup>21</sup> In migraine with aura, this means before the first aura signs and in migraine without aura before the onset of pain. We included only migraine without aura patients. Migraine provocation with GTN typically follows a biphasic pattern; it first induces immediate headache in migraine patients as well as healthy controls, after which migraineurs may develop a delayed headache fulfilling the criteria for migraine without aura within 12 hours (**Fig. 1**).<sup>5</sup> This biphasic pattern limits the applicability of the ICHD-3 criteria for premonitory symptoms.<sup>21</sup> Therefore, in accordance with other provocation studies, the following definition for pharmacological triggered premonitory symptoms was applied: premonitory symptoms are nonheadache symptoms before (preictal) the onset of a provoked migrainous headache.<sup>1,30</sup> Migraine-like attack onset (ictal) was determined according to criteria as used in similar previously published provocation studies<sup>4,6,18,19</sup> as attacks fulfilling either (1) moderate to severe headache (verbal rating scale [VRS]  $\geq 4$ ) fulfilling ICHD-3 criteria C and D for migraine without aura or (2) headache described as mimicking patients usual migraine attack and treated with acute migraine medication.

### 2.4. Questionnaires

In this study, we recorded the presence of 21 possible premonitory symptoms, possible aura symptoms, and a detailed headache assessment including known migrainous headache associated symptoms, verbal pain score, type of pain, and location. Premonitory symptoms included fatigue, yawning, thirst, concentration difficulties, craving for sweets, fluid retention, neck stiffness, face or extremity stiffness, feeling depressed, feeling irritated, decreased appetite, increased appetite, mental restlessness, physical restlessness, decreased urination, altered bowel habits, sleep disturbances, photophobia, phonophobia, nausea, and vomiting. Associated nonheadache symptoms as photophobia, phonophobia, nausea, and vomiting were also listed as part of the headache assessment. After conclusion of the study day in the hospital (5 hours after GTN infusion), participants registered the onset of headache in a headache diary. Participants were also asked for headache fitting migraine-like attack onset in the telephone follow-up  $\pm 3$  days after participation, to determine GTN responder status.

### 2.5. Statistical analysis

Descriptive statistics were reported as mean  $\pm$  SDs or percentages. Differences in mean values were compared between groups using an independent-samples *t* test or Mann-Whitney *U* test for continuous data and a Fisher's exact test for categorical data. In this study, clinical data collected as part of an



**Figure 1.** Schematic headache pattern after the start of the GTN infusion in the 3 study groups. In red, a typical headache pattern for migraine patients who respond to GTN (GTN responders) is shown, combined with typical patterns for migraine patients who do not respond to GTN (GTN nonresponders) in orange and healthy controls in green. Data on the presence of nonheadache symptoms were collected for 5 hours after GTN infusion indicated by solid lines in the headache response and symptom assessments (premonitory and ictal). GTN, glyceryl trinitrate infusion (GTN; 0.5  $\mu$ g/kg/min for 20 minutes).

extensive imaging study was used; therefore, no a priori power calculation was performed. As primary outcome, we investigated the incidence of nonheadache symptoms between GTN responders (developed a migraine-like attack) vs GTN nonresponders and GTN responders vs healthy controls using a Fisher's exact test. Explored intervals included before (preictal) and during the onset of the migraine-like attack (ictal) and over the entire study period (0-5 hours). As GTN nonresponders and healthy controls do not develop a migraine-like, we determined the median interval for the responder group and applied this to the other groups to ensure the number of observations matched between groups for the preictal and ictal intervals. *P*-values < 0.05 were considered to indicate statistical significance and were not adjusted for multiple testing. All statistical analyses were performed using SPSS 23.0 (SPSS, Inc, IBM).

### 3. Results

#### 3.1. Clinical characteristics

In total, we started with  $n = 37$  participants with migraine and  $n = 25$  healthy controls in this study. Four participants were excluded; 3 participants with migraine and 1 healthy control (**Fig. 2**). The healthy control was excluded because of a provoked migraine-like headache. One migraine patient was excluded because we could not classify the provoked headache attack (did not fully fulfill migraine-like headache but could also not be classified as a nonresponder); 2 migraine patients were excluded because GTN infusion was not performed due to claustrophobia as both patients refused further participation after the first scan session. Thus, data from  $n = 34$  participants with migraine and  $n = 24$  healthy controls were suitable for analysis. Participants with migraine and healthy controls were of similar age ( $34.1 \pm 8.2$  vs  $35.2 \pm 9.1$  years) and body mass index ( $22.9 \pm 2.6$  vs  $23.2 \pm 2.7$ ). Among the clinical variables, there were no significant differences between groups except for the average headache days per month, which was higher for participants with migraine (**Table 1**).

#### 3.2. Migraine-like attack provocation

Twenty-eight participants with migraine (82.4%) experienced a migraine-like attack after GTN infusion and were defined as responders. Migraine-like attack characteristics of GTN responders are shown in e-table 1, supplementary materials (available at <http://links.lww.com/PAIN/B2>), reported onset ranged between 45 and 345 minutes. Headache experienced by the study groups during and after GTN infusion is shown in

**Figure 3.** Glyceryl trinitrate responders were significantly older at disease onset ( $17.5 \pm 4.7$  vs  $11.2 \pm 6.7$ ), had a higher disability expressed in migraine disability assessment (MIDAS) and HIT-6 scores, and experienced more migraine days per month ( $5.0 \pm 2.7$ ) compared with nonresponders, see **Table 1**.

#### 3.3. Premonitory and ictal nonheadache symptoms

To inspect onset after GTN, symptoms were summed per assessment (0-5 hours) for responders and healthy controls (**Fig. 4**) and nonresponders and responders (e-figure 1, supplementary materials, available at <http://links.lww.com/PAIN/B2>). Yawning, fatigue, thirst, neck stiffness, concentration difficulties, nausea, and photophobia were among the earliest frequently reported symptoms. Yawning, nausea, and photophobia appeared to be more specific for responders, and concentration difficulties were even exclusively reported by responders. Fatigue, thirst, and neck stiffness were regularly reported by both responders and healthy controls in the first hours after GTN. Symptoms most frequently reported by responders included fatigue (82.1%), photophobia (82.1%), nausea (75.0%), yawning (64.3%), phonophobia (60.7%), thirst (57.1%), and neck stiffness (53.6%), see e-table 2, supplementary materials (available at <http://links.lww.com/PAIN/B2>). For symptoms reported by each individual participant, see e-figures 2 (responders), 3 (nonresponders), and 4 (controls), supplementary materials (available at <http://links.lww.com/PAIN/B2>).

Almost all GTN responders (92.9%) reported at least one of the 21 premonitory symptoms after GTN infusion before the onset of migraine-like headache compared with 100% of GTN nonresponders and 54.2% of healthy controls. Responders reported concentration difficulties ( $P = 0.011$ ), yawning ( $P = 0.009$ ), nausea ( $P = 0.028$ ), and photophobia ( $P = 0.001$ ) more frequently compared with controls (**Table 2**). To validate our findings, we performed a sensitivity analysis excluding 2 controls with a high VRS at the end of the study day (**Fig. 3**); this had only marginal effects and did not affect our main findings except for nausea (which did not reach significance [ $P = 0.060$ ]) due to reduced power as none of excluded controls suffered from nausea (data not shown). No significant differences in reported symptoms were found between responders and nonresponders apart from reported associated symptoms during the provoked migrainous headache phase with nausea, photophobia, and phonophobia in the responders, which is logical as these symptoms form part of the criteria for defining a provoked migraine-like attack. The significant premonitory symptoms persisted ictally, and fatigue, neck stiffness, decreased appetite,

**Table 1**  
**Clinical characteristics of the healthy controls and migraine patients, subdivided GTN responders and GTN nonresponders.**

	Healthy controls (n = 24)	Migraine patients (n = 34)	GTN responders (n = 28)	GTN nonresponders (n = 6)
Age (y)	35.2 ± 9.1	34.1 ± 8.2	34.9 ± 8.4	30.3 ± 6.4
BMI (kg/m <sup>2</sup> )	23.2 ± 2.7	22.9 ± 2.6	23.2 ± 2.7	21.6 ± 1.4
Systolic blood pressure (mm Hg)	121.9 ± 11.9	119.2 ± 13.6	120.5 ± 13.4	112.8 ± 14.0
Diastolic blood pressure (mm Hg)	78.3 ± 9.4	80.2 ± 9.6	80.4 ± 9.8	78.8 ± 9.3
Heart rate (bpm)	69.7 ± 10.9	68.2 ± 8.4	68.0 ± 8.9	68.7 ± 6.2
Glucose (mmol/L)	4.7 ± 0.7	4.6 ± 0.6	4.7 ± 0.5	4.4 ± 0.7
Headache days per month	0.6 ± 0.5	6.5 ± 3.5	6.8 ± 3.7	5.5 ± 2.1
Migraine days per month		4.6 ± 2.7	5.0 ± 2.7	2.7 ± 0.8
Average duration-treated attack (h)		16.3 ± 23.6	19.1 ± 25.1	3.0 ± 4.4
Average duration-untreated attack (h)		42.0 ± 25.3	45.8 ± 25.4	25.0 ± 18.1
Age of onset (y)		16.4 ± 5.6	17.5 ± 4.7	11.2 ± 6.7
MIDAS		16.6 ± 17.7	19.0 ± 18.4	5.5 ± 7.3
HIT-6 score		61.7 ± 4.2	62.5 ± 3.8	58.3 ± 4.3

Values are the mean ± SD.  
 BMI, body mass index; GTN, glyceryl trinitrate; HIT-6, Headache Impact Test-6; and MIDAS, migraine disability assessment.

vomiting, and phonophobia were also reported more frequently by responders compared with controls during this phase (Table 2).

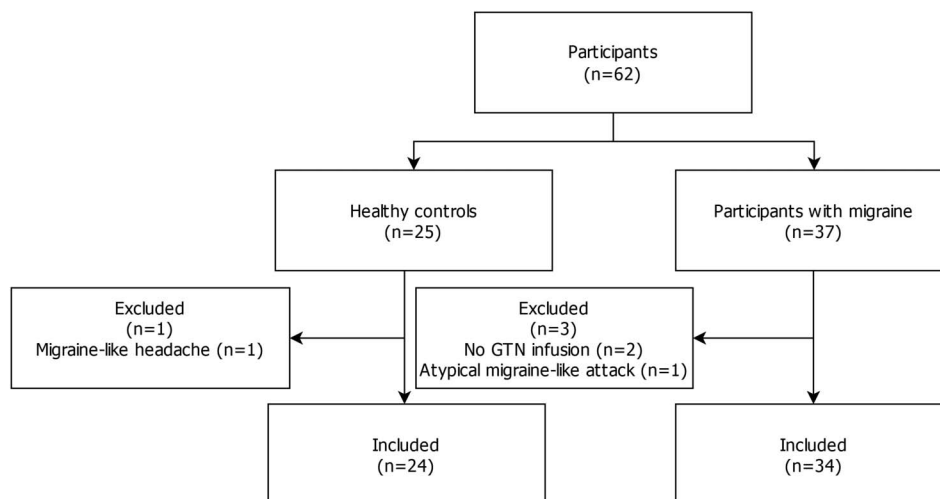
**3.4. Symptoms in relation to migraine-like attack onset**

Of the 4 identified specific symptoms, we assessed which symptom was reported first by each GTN responder (Fig. 5A). Yawning and nausea were reported as initial specific premonitory symptom by 8 responders, followed closely by photophobia (n = 7), while concentration difficulties were reported the fewest times (n = 4). To inspect the onset of yawning, concentration difficulties, nausea, and photophobia with respect to onset of the migraine-like attack, we plotted the interquartile range (middle 50%) of the average reported time across responders. Yawning is reported first followed by nausea, photophobia, and concentration difficulties (Fig. 5B). As the reaction to GTN often follows a biphasic headache pattern (an immediate headache that

resides, and later, a migraine-like headache develops, Fig. 1), we checked whether these symptoms were (in)dependent from headache. Fourteen responders with pain-free intervals after GTN infusion ended were inspected and checked for the occurrence of these symptoms in the postinfusion phases without headache. Yawning, nausea, and photophobia were also reported in the headache-free intervals, while concentration difficulties were not mentioned in a pain-free state.

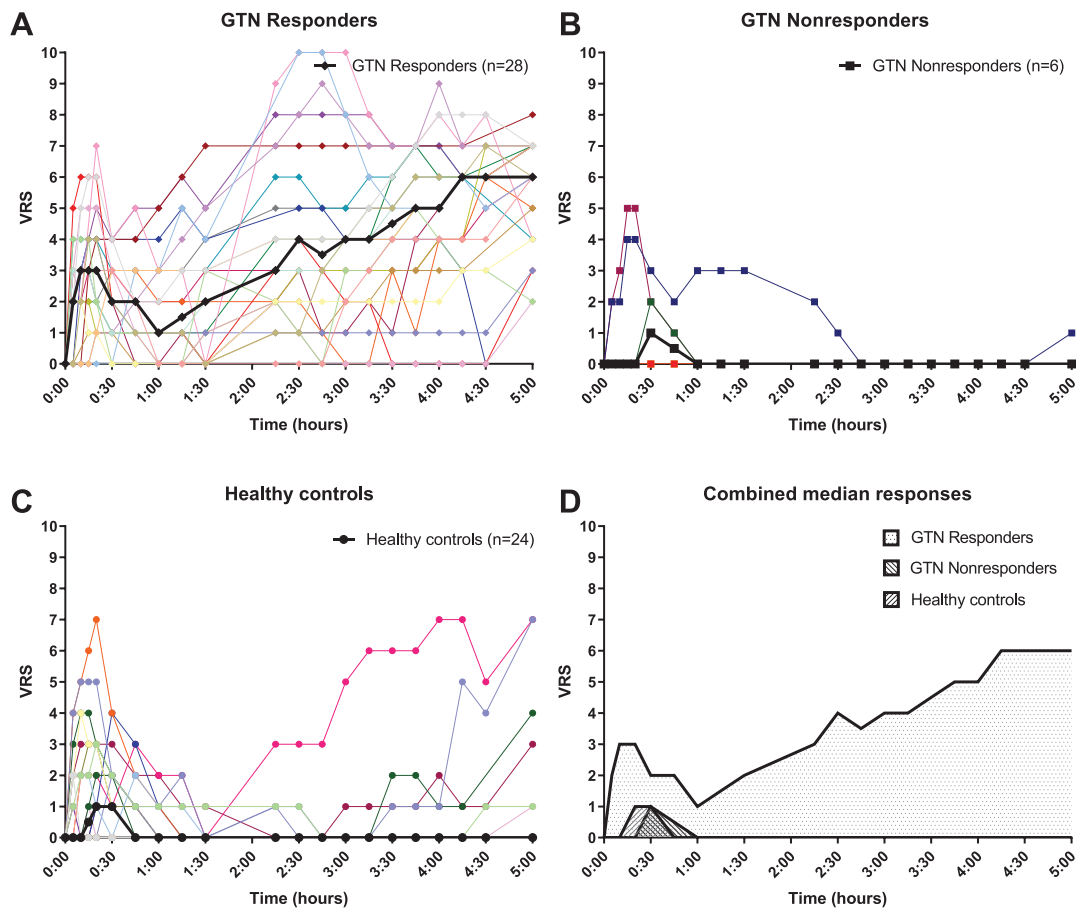
**4. Discussion**

We performed a systematic assessment into the specificity and development of premonitory symptoms in GTN-provoked migraine-like attacks. Because of the inclusion of a control group and an extensive prospective assessment under matched conditions, we were able to show for the first time that concentration difficulties were exclusively reported by those who developed a migraine-like attack. Yawning and nausea were



**Figure 2.** Study flowchart. GTN, glyceryl trinitrate.





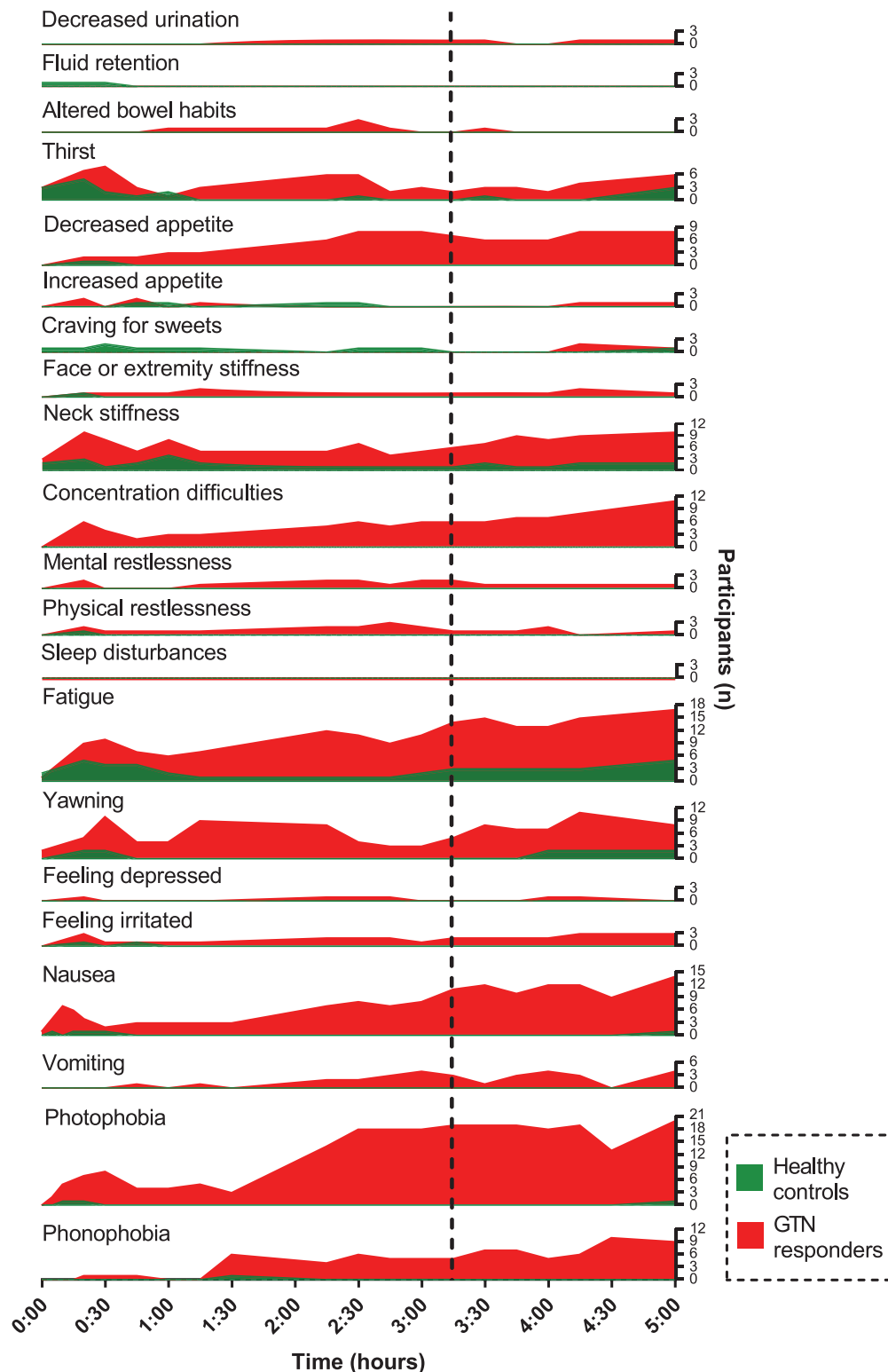
**Figure 3.** Verbal rating scale over time. (A) Individual and median verbal rating scores are depicted for participants with migraine developing a migraine-like attack after glyceryl trinitrate (GTN responders; individual cases = various colors with diamonds, median = black line with diamonds), (B) participants with migraine who did not develop an attack (GTN nonresponders; individual cases = various colors with squares, median = black line with squares), and (C) healthy controls (individual cases = various colors with circles, median = black line with circles). (D) Median verbal rating scores are depicted for GTN responders (dots), GTN nonresponders (left diagonal lines), and healthy controls (right diagonal lines) after glyceryl trinitrate. Note, 2 controls reported a high VRS of 7 at the end of the study (see C). Clinically, there was a discrepancy between the reported subjective VRS and how this objectively was interpreted by the investigator, and the headache did not fulfill criteria for migraine-like headache. GTN, glyceryl trinitrate; VRS, verbal rating scale.

the earliest symptoms reported, followed by photophobia and concentration difficulties that occurred nearer to attack onset. Neck stiffness, fatigue, decreased appetite, vomiting, and phonophobia though associated with migraine-like headache lacked specificity preictally.

Having a closer look at the 4 most specific premonitory symptoms identified in the current study, excessive yawning is the earliest reported symptom in responders relative to attack onset, although there is considerable overlap between 4 identified symptoms, and on participant level, nausea and photophobia were also reported frequently as initial specific symptom. The anatomical basis of yawning in migraine is typically linked to the hypothalamus,<sup>24</sup> which has been shown to be involved in spontaneous<sup>9,41</sup> and provoked attack onset in imaging studies.<sup>30</sup> Nausea, also reported early, might also be linked to this same brain region<sup>24,33</sup> but may also be linked to the rostral dorsal medulla and the periaqueductal gray.<sup>32</sup> Apart from imaging evidence, the circadian rhythmicity of attacks<sup>2,3,36</sup> and the association with the menstrual cycle<sup>10,29,35</sup> also point to hypothalamic involvement in migraine.<sup>33</sup> Furthermore, on a neurotransmitter level, the dopaminergic system might be a driving force because dopaminergic agonists have been reported to increase among others yawning and nausea in migraine patients, while antagonists are used to treat nausea.<sup>34</sup> Photophobia, also

identified in the current study, is also among the early reported symptoms and has been suggested to involve the thalamus or cortical areas of the brain.<sup>24,31</sup> Projections between the posterior hypothalamus and thalamus have been previously reported.<sup>22,33</sup> This is consistent with brain activation of i.a. the thalamus and occipital cortex as shown in the late premonitory phase in GTN-triggered attacks.<sup>30</sup> Concentration difficulties with a late onset, and likely involving cortical areas, are the most specific because it is only reported by responders.

Cognitive dysfunction in general, difficulty with focusing, concentration, speech, and reading, is among the most frequently reported complaint during the premonitory phase across studies.<sup>13</sup> This impairment may remain during the migraine headache and postdromal phase and has been objectively measured to affect migraineurs during attacks.<sup>43</sup> Interictal studies yield inconsistent results due to differences in clinical characteristics, recruitment methodology, migraine preventative usage, and comorbidities.<sup>14,43</sup> In our study, concentration difficulties was a unique premonitory symptom only reported in migraine patients with a provoked attack. Notably, also our GTN nonresponders and controls who experienced infusion headache never reported concentration problems. Difficulty in concentrating has been reported for in other headache types such as cluster headache and tension-type



**Figure 4.** Reported nonheadache symptoms over time (0-5 hours) by GTN responders (red) and healthy controls (green). The reported median onset for migraine-like attacks (181 minutes; making this after the questionnaire taken at 195 minutes after GTN infusion) is depicted by a dashed line, illustrating the preictal and ictal period. GTN, glyceryl trinitrate.

headache, but in these conditions, it was purely related to severe pain during the headache,<sup>43</sup> while in migraine concentration difficulty is frequently reported in the premonitory phase in the absence of headache.<sup>11,12</sup> However, we also noticed that concentration difficulties were temporally the closest to the

migraine headache onset in our study when a mild headache was already developing. Importantly, concentration difficulties were exclusively reported by those who developed a migraine-like attack and may be a good early warning signal that may be helpful in clinical practice for patients.

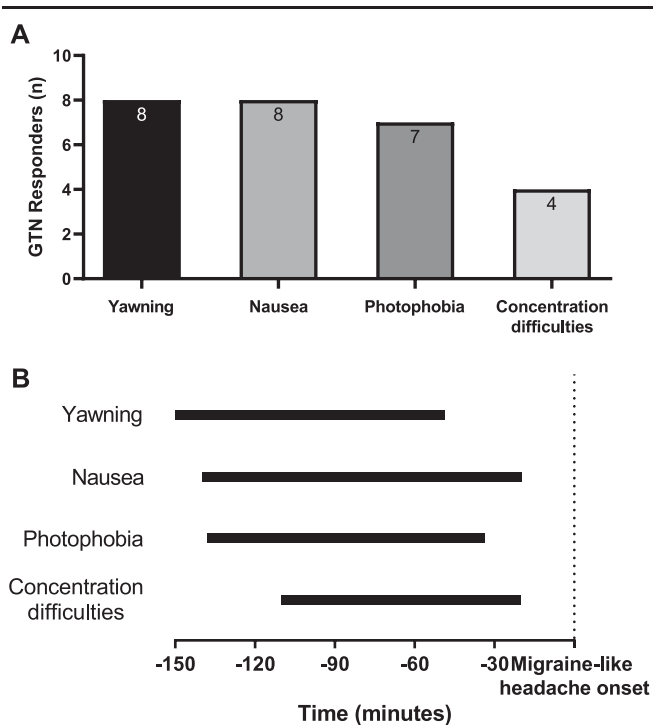
**Table 2**

**Nonheadache symptoms reported after the start of GTN infusion.**

Nonheadache symptoms after GTN (0-5 h)	Premonitory symptoms					Ictal symptoms				
	GTN responders (n = 28)	Healthy controls (n = 24)	GTN nonresponders (n = 6)	Responders vs controls, <i>P</i>	Responders vs nonresponders, <i>P</i>	GTN responders (n = 28)	Healthy controls (n = 24)	GTN nonresponders (n = 6)	Responders vs controls, <i>P</i>	Responders vs nonresponders, <i>P</i>
Any nonheadache symptom	92.9 (26)	54.2 (13)	100.0 (6)	<b>0.003</b>	1.000	89.3 (25)	29.2 (7)	100.0 (6)	<b>&lt;0.001</b>	1.000
Decreased urination	0 (0)	0 (0)	0 (0)	n/a	n/a	3.6 (1)	0 (0)	0 (0)	1.000	1.000
Fluid retention	0 (0)	4.2 (1)	0 (0)	0.462	n/a	0 (0)	0 (0)	0 (0)	n/a	n/a
Altered bowel habits	3.6 (1)	0 (0)	0 (0)	1.000	1.000	10.7 (3)	0 (0)	0 (0)	0.240	1.000
Thirst	42.9 (12)	29.2 (7)	33.3 (2)	0.391	1.000	28.6 (8)	12.5 (3)	0 (0)	0.190	0.297
Decreased appetite	17.9 (5)	4.2 (1)	0 (0)	0.199	0.559	35.7 (10)	0 (0)	0 (0)	<b>0.001</b>	0.148
Increased appetite	10.7 (3)	12.5 (3)	33.3 (2)	1.000	0.205	3.6 (1)	0 (0)	0 (0)	1.000	1.000
Craving for sweets	0 (0)	12.5 (3)	0 (0)	0.092	n/a	10.7 (3)	4.2 (1)	0 (0)	0.615	1.000
Face or extremity stiffness	7.1 (2)	4.2 (1)	16.7 (1)	1.000	0.453	7.1 (2)	0 (0)	16.7 (1)	0.493	0.453
Neck stiffness	46.4 (13)	20.8 (5)	0 (0)	0.080	0.062	42.9 (12)	12.5 (3)	0 (0)	<b>0.030</b>	0.069
Concentration difficulties	25.0 (7)	0 (0)	0 (0)	<b>0.011</b>	0.306	39.3 (11)	0 (0)	0 (0)	<b>&lt;0.001</b>	0.145
Mental restlessness	7.1 (2)	0 (0)	16.7 (1)	0.493	0.453	14.3 (4)	0 (0)	16.7 (1)	0.115	1.000
Physical restlessness	17.9 (5)	4.2 (1)	0 (0)	0.199	0.559	14.3 (4)	0 (0)	0 (0)	0.115	1.000
Sleep disturbances	0 (0)	0 (0)	0 (0)	n/a	n/a	0 (0)	0 (0)	0 (0)	n/a	n/a
Fatigue	42.9 (12)	25.0 (6)	33.3 (2)	0.245	1.000	71.4 (20)	20.8 (5)	50.0 (3)	<b>&lt;0.001</b>	0.363
Yawning	53.6 (15)	16.7 (4)	50.0 (3)	<b>0.009</b>	1.000	46.4 (13)	12.5 (3)	50.0 (3)	<b>0.015</b>	1.000
Feeling depressed	3.6 (1)	0 (0)	0 (0)	1.000	1.000	3.6 (1)	0 (0)	0 (0)	1.000	1.000
Feeling irritated	10.7 (3)	8.3 (2)	16.7 (1)	1.000	0.559	14.3 (4)	0 (0)	0 (0)	0.115	1.000
Nausea	28.6 (8)	4.2 (1)	33.3 (2)	<b>0.028</b>	1.000	71.4 (20)	4.2 (1)	16.7 (1)	<b>&lt;0.001</b>	<b>0.021</b>
Vomiting	0 (0)	0 (0)	0 (0)	n/a	n/a	39.3 (11)	0 (0)	0 (0)	<b>&lt;0.001</b>	0.145
Photophobia	42.9 (12)	4.2 (1)	16.7 (1)	<b>0.001</b>	0.370	78.6 (22)	4.2 (1)	0 (0)	<b>&lt;0.001</b>	<b>0.001</b>
Phonophobia	17.9 (5)	4.2 (1)	0 (0)	0.199	0.559	60.7 (17)	0 (0)	0 (0)	<b>&lt;0.001</b>	<b>0.018</b>

Values are the numbers and percentages. *P* values calculated with the Fisher's exact test. *P* values depicted in bold indicate a statistical significant results at the 0.05 level. GTN, glyceryl trinitrate; n/a, not applicable.





**Figure 5.** Timing of premonitory symptoms. (A) Premonitory symptoms reported first. Depicted is the number of GTN responders who reported a particular specific premonitory symptom first. In case 2 symptoms were reported simultaneously (P23 and P37, see e-figure 2, <http://links.lww.com/PAIN/B2>), both symptoms were plotted. Two GTN responders (P19 and P24) not reporting premonitory symptoms, and P3 that reported none of the identified specific premonitory symptoms, were not included (see e-figure 2, <http://links.lww.com/PAIN/B2>). (B) Timing of premonitory symptoms relative to onset of migraine-like headache. Depicted are the interquartile ranges plotted for yawning, nausea, photophobia, and concentration difficulties composed of all responders that reported these symptoms relative to the onset of the migraine-like headache attacks. GTN, glyceryl trinitrate.

Our results indicate that the hypothalamus (yawning and nausea), the brainstem (nausea), thalamus (photophobia), and cortical areas (photophobia and concentration difficulties) are involved in the premonitory phase with concentration difficulties being unique to GTN responders. Whether the hypothalamus is indeed activated first, which is suggested on a group level, cannot be reliably deduced from the current study because nausea (also attributed to the brainstem), photophobia, and concentration difficulties are also reported as initial symptoms by a considerable number of GTN responders. Although all responders reported at least one of the 4 identified symptoms, excluding the 2 responders without premonitory symptoms and 1 responder that reported none of the specific symptoms, not all 4 symptoms were present in each participant. This may suggest different brain structures, in different migraineurs, in different temporal sequences may be involved in the premonitory phase of migraine. To investigate affected brain structures and brain networks, future provocation studies might use detailed imaging methods (such as [resting state] functional magnetic resonance imaging) to follow-up the sequence of reported symptoms. Interestingly, premonitory symptoms persist during ictal and postictal phases, as shown in this study and in literature,<sup>11,12,17</sup> substantially lengthening the actual attack duration from 4 to 72 hours (headache) and making the headache only one of the symptoms in the intricate cascade. This chain of symptomatology has led to the hypothesis of an oscillating system of complex

brain networks influencing the susceptibility threshold of sensory signals and bodily functions toward the onset of migrainous headache.<sup>8,34,38</sup>

Previous studies with GTN as a pharmacological trigger reported many premonitory symptoms before the onset of migraine-like headache.<sup>1,23,30</sup> However, several symptoms such as neck stiffness, tiredness/fatigue, thirst, feeling moody/irritated, and phonophobia were also frequently reported by our healthy volunteers and thus lack specificity as early warning signal for onset of a migrainous headache. Whether the reported symptoms present in half of the controls after GTN infusion represent other brain areas or networks, incompletely activated network(s), GTN substance-related symptomatology, or symptoms reported due to the repeated and intensive interviews during the study procedure, cannot be deduced with certainty as no placebo group was included. However, we consider the inclusion of a control group as one of the strengths of our study allowing to identify symptoms specifically associated with migraine. For case-control studies, there is a potential risk that healthy controls might experience migraine attack(s) in the future; this is especially true for young participants. However, although peak prevalence in females is around 40 years, most female patients manifest before the age of 35.<sup>26,28</sup> Glyceryl trinitrate has been shown to be such a potent trigger for migraine that it is also able to trigger migraine-like attacks in controls with a familial occurrence of migraine.<sup>1</sup> Controls in our study, apart from one participant who was excluded from the analysis, did not develop migraine-like headache. We feel, therefore, that it is less likely, compared with other case-control studies, that our controls will be at risk to develop migraine in the future. Our control group consisted of age-matched healthy female volunteers, minimizing possible age and sex influences. Because all participants followed the same study day protocol and stayed in the same hospital rooms, environmental influences were also minimized. Furthermore, to the best of our knowledge, this is the first study to systematically investigate (using an extensive questionnaire) the occurrence of premonitory symptoms in a population of migraine patients not selected for the occurrence of premonitory symptoms. We also elaborately assessed timing of symptom onset in this study. It should be noted that because this study was part of larger imaging study, we could not gather information on the presence of nonheadache symptoms while participants were being scanned. However, because our assessment was extensive outside the 2 scan moments (every 15 minutes) and most symptoms were present on multiple assessments, we expect no symptoms were missed. A limitation in our study, as in other GTN model studies, is that nonsignificant findings for the comparison between responders and nonresponders might be caused by the low number of nonresponders because of the large response rate (>80%).<sup>1,6,23</sup> Second, we included only females and only participants with migraine without aura, which may limit the generalizability of our results, and lastly, we did not ask the patients who experienced premonitory symptoms whether the induced symptoms mimicked their usual symptoms because this was not the interest of our study.

In conclusion, our findings support the view that GTN is able to provoke the naturally occurring premonitory symptoms of which yawning, nausea, photophobia, and concentration difficulties are most distinctly predicting an impending GTN-induced migraine-like headache, indicative of specific pathophysiological mechanism underlying the beginning of attacks. Importantly, concentration difficulties were exclusively reported by those who developed a migraine-like attack. Specific early warning signals may be helpful in clinical practice for patients and their treating

physicians to prevent occurrence of full blown attacks by early treatment strategies.

### Conflict of interest statement

M.D. Ferrari reports grants and consultancy or industry support from Medtronic, Novartis, Amgen, Lilly, Teva, electroCore, and independent support from NWO, ZonMW, NIH, European Community, and the Dutch Heart Foundation. G.M. Terwindt reports consultancy support from Novartis, Amgen, Lilly, Teva, and independent support from NWO, ZonMW, NIH, Dutch Heart Foundation, and Dutch Brain Foundation. The remaining authors have no conflicts of interest to declare.

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### Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at <http://links.lww.com/PAIN/B2>.

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