Sumatriptan prevents central sensitization specifically in the trigeminal dermatome in humans

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Abstract

Background: The exact mechanism and site of action of triptans in aborting migraine attacks remain under debate. We hypothesized that the clinical efficacy of triptans lies in aborting central sensitization and focused on the question of why triptans are headache specific, that is highly effective in migraine and cluster headache and ineffective in extracephalic pain.

Methods: Forty healthy participants were enrolled in this double-blinded, randomized, placebo-controlled study. The effect of sumatriptan (n = 20) versus placebo (n = 20) was investigated in a trigeminal (V1) versus an extracephalic dermatome (forearm) using a topical capsaicin sensitization model. Capsaicin-induced primary and secondary hyperalgesia were evaluated using quantitative sensory testing.

Results: After capsaicin application, primary hyperalgesia developed in both the sumatriptan and placebo groups in both dermatomes. However, sumatriptan exclusively prevented secondary hyperalgesia in the V1 dermatome but not on the forearm. Placebo exerted no effects on secondary hyperalgesia in both trigeminal and extracephalic dermatomes. Additionally, sumatriptan reduced the flare size exclusively in the V1 dermatome.

Conclusions: Our data suggest that sumatriptan reduces central sensitization (secondary hyperalgesia) without modulating peripheral sensitization (primary hyperalgesia) in a human pain model of capsaicin-induced sensitization. Moreover, despite a systemic administration of sumatriptan, the modulatory effects are trigeminal specific, echoing the clinical effect of triptans in aborting headache attacks, but not extracephalic pain.

Significance: Our data suggest that triptans exert their efficacy by suppressing central sensitization. By revealing a dermatome-specific modulation, our study demonstrates a previously unrecognized interaction between the pharmacodynamics of triptans and the trigeminal nociceptive system that provides new insight into how triptans may work in aborting headache attacks.

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1 | INTRODUCTION

Triptans are first-line therapy to treat migraine (Evers et al., 2009) and cluster headache attacks (May et al., 2006) and act as agonists for serotonin 5-HT_{1B/1D} receptors. 5-HT_{1B} receptors locate on the arterial smooth muscle, but the sumatriptan-induced vasoconstriction is not associated with migraine symptoms improvement in a temporal sense (Limmroth et al., 1996). Both 5-HT_{1B} and 5-HT_{1D} receptors are present in trigeminal ganglia, but only 5-HT_{1D} receptors were identified at the trigeminal nerve ending projecting to the dura peripherally and to the trigeminal nucleus caudalis (TNC) centrally (Longmore et al., 1997). Despite its well-established efficacy, the mechanism and site of action remain under debate. At least three different sites of action have been proposed. (i) The peripheral mechanism—calcitonin gene-related peptide (CGRP) colocalizes with 5-HT_{1B/1D} receptors in trigeminal ganglion (Ma et al., 2001). In an animal model, trigeminal ganglion stimulation elevated the CGRP level in the external jugular vein; in humans, the CGRP level increased in spontaneous migraine attacks (Goadsby et al., 1990). Triptan may exert its efficacy by inhibiting CGRP release from the peripheral nerve terminals—the administration of sumatriptan not only subsides the migraine attack but also reduces CGRP levels (Goadsby & Edvinsson, 1993). (ii) The central mechanism—naratriptan injected into the periaqueductal grey inhibits dura-evoked nociceptive response in the TNC (Bartsch et al., 2004); treatment with sumatriptan is associated with decreased central 5-HT_{1B} receptor binding in the brain (Deen et al., 2019). (iii) The synaptic gap between the cell body of the secondary sensory neurons (central) and the axonal terminals of primary sensory neurons (peripheral) (Levy et al., 2004). In an animal model, triptans reduced central sensitization without altering peripheral sensitization by reducing neurotransmitters release from the afferents via a presynaptic mechanism (Levy et al., 2004).

The third model—the synaptic gap as a site of action was based primarily on animal studies (Bartsch et al., 2004; Levy et al., 2004). Indirect evidence suggests that it also applies to humans. Burstein et al. demonstrated sequential development of cephalic and extracephalic allodynia—an indicator of central sensitization (Burstein et al., 2000). Notably, synaptic plasticity is critical in the generation of central sensitization (Woolf, 2011). It has been therefore proposed that once the central sensitization is well established (with the presence of allodynia), triptans no longer work as well as before the establishment of allodynia (Diamond et al., 2007; Levy et al., 2004). However, other studies suggest that the efficacy of triptans is associated with pretreatment pain intensity, not

2 | METHODS

2.1 | Study design

We conducted a double-blind randomized, placebo-controlled study to investigate the effects of pre-emptively administered subcutaneous sumatriptan on capsaicin-induced primary hyperalgesia, secondary hyperalgesia and the areas of flare, as well as secondary mechanical hyperalgesia. These parameters were measured in the first branch (V1) of the trigeminal nerve and an extratrigeminal region (forearm) in healthy volunteers.

2.2 | Ethics approval and consent to participate

The study was approved by the local Ethics Committee of the Medical Chamber of Hamburg (protocol number PV3814) and conformed to the Declaration of Helsinki. All participants gave written informed consent.

2.3 | Subjects

Healthy participants were recruited among medical students of Hamburg University. Only subjects between 18 and 65 years of age were eligible. Exclusion criteria included chronic pain disorder, including primary and secondary headaches or extracephalic pain, acute pain within the last 4 weeks, any long-term medication apart from oral contraceptives, intake of analgesics or triptans within the last 72 h, pregnancy and lactation, alcohol or drug addiction, relevant medical, neurological or psychiatric disorders. Forty healthy subjects (21 male and 19 female, mean age 24.1 ± 1.9 years, range 21–30 years) were recruited for this study.

2.4 | Experimental design

Baseline quantitative sensory testing (QST) readings were obtained for all parameters before the administration
of sumatriptan except the area of flare and secondary hyperalgesia. Subcutaneous sumatriptan/placebo (20 subjects each) was administered in a pre-emptive fashion 20 min before capsaicin was applied to both the forehead (V1) and the ventral forearm to ensure a maximum plasma concentration of sumatriptan with a $T_{\text{max}}$ of 0.17 h (Duquesnoy et al., 1998). The following variables were used as outcomes of putative effects of sumatriptan on capsaicin-induced changes after removal of the capsaicin patch: (i) the mapping of the areas of flare and secondary hyperalgesia to punctuate stimuli; (ii) warm detection thresholds (WDH) within the zone of capsaicin application; (iii) primary heat hyperalgesia (PHH) within the zone of capsaicin application; (iv) secondary hyperalgesia adjacent to the area of capsaicin application by mechanical pain sensitivity (MPS) and dynamic mechanical allodynia (DMA). The area of capsaicin application was defined as the test site, and the corresponding area on the contralateral side was defined as the control site (see Figure 1 for further details). Somatosensory testing always started on the test site of V1 and continued on the contralateral control site for each modality in the following order: WDT, PHH, MPS/DMA for QST, mapping of flare and mapping of the secondary hyperalgesia. The identical sequence was repeated at the ventral forearm immediately after removing the capsaicin patch. This protocol has been validated and published elsewhere (Jürgens et al., 2014).

### 2.5 Intervention

Participants received either 6 mg sumatriptan or 0.9% normal saline in a volume of 0.5 ml in a pseudorandomized fashion. Pseudorandomization was balanced for the side of injection (right or left) and gender (female or male) in a 50:50 ratio on a list to which only TJ had access to maintain allocation concealment. To maintain blinding, a physician without any further involvement in the process of data acquisition transferred either 0.5 ml saline out of 10 ml plastic vials (B. Braun Melsungen AG) or 0.5 ml of commercially available sumatriptan (6 mg sumatriptan equivalent to 8.4 mg sumatriptan succinate in 0.5 ml sterile water) supplied as an autoinjector (IMIGRAN Inject, GlaxoSmithKline) into a 1-ml syringe fitted with a 30G needle. Both the examiner and the participants remained unaware of the allocation to either sumatriptan or saline. In the absence of contraindications to sumatriptan, sumatriptan (and placebo, respectively, saline) were injected either into the lateral upper arm or lateral upper thigh after local disinfection with an alcoholic solution.

### 2.6 Conditioning stimulus

Alcoholic capsaicin solution with a concentration of 0.25% and 1% supplied by the hospital pharmacy (0.125 g of capsaicinoid in 49.875 mg ethanol 70% and 0.5 g of ethanol 96%, respectively) was applied. The capsaicin concentration and the concentration of ethanol were chosen to generate moderate pain and to avoid local skin necrosis. The application time was 10 s to ensure the maximal effect of the capsaicin concentration used.

![Figure 1](image_url) **Figure 1** Experimental design. (a) Schematic illustration of the experimental design. Test and control sites are randomized (right: left = 1:1). (b) Detailed design of the sensory testing algorithm. Cap: Capsaicin, MAP: mapping, MAP-FL: mapping of flare, MAP-SH: mapping of secondary hyperalgesia, MPS: mechanical pain sensitivity and dynamic mechanical allodynia, PHH: primary heat hyperalgesia, QST: Quantitative Sensory Testing, V1: forehead, WDT: warm detection thresholds.
capsaicinoid in 49.5 mg ethanol 70%) was used to soak a filter paper sized 16x16 mm which was placed at V1 (0.25%) for 5 min and the ventral forearm (1%) for 20 min. Whereas the individual difference in the size of flare and secondary hyperalgesia is high, the concentration and stimulus duration were based on the results of the propaedeutic experiments, in which a consistent area of flare and secondary hyperalgesia could have been established in most participants.

2.7 | Quantitative sensory test parameters

2.7.1 | Warm detection thresholds (WDT)

Warm detection thresholds were determined with a computerized thermal sensory testing device (TSA-II NeuroSensory Analyzer, MEDOC Ltd.) with a contact area of 16x16 mm². A baseline of 32°C was maintained until the temperature of the probe ramped with 1°C/s. WDT was recorded three times using the method of limits (Rolke, Magerl, et al., 2006) and the arithmetic mean was calculated for further analysis.

2.7.2 | Primary heat hyperalgesia (PHH)

To determine the extent of primary heat hyperalgesia, brief heat stimuli were applied to the test and the control site with the thermal sensory testing device (TSA-II NeuroSensory Analyser, Medoc Ltd.) using a contact area of 16x16 mm². PHH has been found to be more sensitive than heat pain thresholds in detecting primary heat hyperalgesia (Jürgens et al., 2014). The probe maintained a constant temperature of 40°C and was applied manually to the skin of the control and test sites for 1 s. Subjects were asked to rate the perceived pain on a numeric rating scale from 0 (no pain) to 100 (worst imaginable pain). The arithmetic mean of 3 successive ratings was taken, separated by an interstimulus interval of 10 s to prevent sensitization elicited by the thermal stimulus itself. The conditioning effect of capsaicin was determined as the difference in pain ratings for the test and control side (Jürgens et al., 2014).

2.7.3 | Mechanical pain sensitivity to pin-prick stimuli and dynamic mechanical allodynia

Both MPS and DMA were examined in an area approximately 1 cm periphery to the area of capsaicin application. Of note, our previous work has demonstrated that the increase of suprathreshold pain rating to thermal stimuli in this area is statistically insignificant (lack of primary hyperalgesia) (Jürgens et al., 2014). MPS was tested using a calibrated set of seven custom-made pinprick stimulators (The Pinprick, MRC Systems). Stimulus intensities increase in an ascending geometrical row (8, 16, 32, 64, 128, 256 and 512 mN) and the stimulators have a flat contact area of 0.25 mm² in diameter which have been shown to reliably activate cutaneous nociceptors (Slugg et al., 2000). DMA is defined as pain to normally innocuous mechanical stimuli and was examined by light stroking with a cotton wisp (3 mN), a cotton wool tip fixed to an elastic strip (100 mN) or a soft brush (Somedic SENSE Lab Brush, Sweden; 200–400 mN). Three sequences were applied subsequently in which all seven pinprick stimuli and three intensities of light stroking were administered in a pseudorandomized order following the DFNS protocol (Rolke, Baron, et al., 2006). The participants were asked to rate the perceived pain on a numeric rating scale from 0 (no pain) to 100 (worst imaginable pain) after each stimulus (Rolke, Magerl, et al., 2006). Ratings were then transformed into the decadic logarithm. To avoid a loss of zero pain ratings, a small constant (0.1) was added to all ratings before log transformation (Magerl et al., 1998). MPS was calculated as the geometric mean of all pain ratings for pinprick stimuli, and DMA as the geometric mean of all pain ratings to light stroking.

2.8 | Mapping of secondary hyperalgesia and flare

The area of secondary hyperalgesia induced adjacent to the site of capsaicin application was determined with a calibrated von Frey hair (Optihair2, Marstock Nervtest) which delivers a punctuate stimulus with a force of 256 mN with a blunt contact area (diameter of 0.5 cm). Mapping of secondary hyperalgesia started well outside the assumed hyperalgesic area. The von Frey hair was gently pressed onto the skin along two predefined trajectories meeting in the centre of the test or control area (i.e. the area of primary hyperalgesia) perpendicular to each other in steps of 5 mm. The subjects were asked to indicate when the sensation of touch or pressure changed to a painful sensation, which was marked as the turning point. Subsequently, the distance of the turning point to the trajectories’ intersection was measured in mm and the mean was calculated for each trajectory. As the area of secondary hyperalgesia regularly had an elliptical shape, it was estimated in mm² with the following formula: π*a*b (a: semi-major axis, b: semi-minor axis). The external boundary of a visible
flare was marked with a felt-tip pen and transferred to a transparent sheet, which was then digitalized. The area of the flare was determined with an open-source software (ImageJ 1.48, National Institutes of Health, USA, http://rsb.info.nih.gov/ij/) in mm².

2.9 Data evaluation and statistics

All data except ratings to pinprick stimuli and light stroking were analysed as raw data. MPS and DMA were transformed into the decadic logarithm as described above. Mean values and standard error of the mean (SE) were calculated. Differences between groups, body regions and over time were examined by means of an analysis of variance for repeated measures (RM-ANOVA). If the assumption of sphericity was violated in Mauchly’s Test, Greenhouse–Geisser correction was applied. For post hoc tests and pairwise comparisons, t-tests were used. Results with p < 0.05 were regarded as significant. Statistical analysis was done with SPSS 21 (IBM Corporation), and graphs were prepared with Graph Pad Prism 5.0 (GraphPad Software, Inc.).

3 RESULTS

3.1 Baseline QST parameters

There were no baseline differences in QST parameters, that is WDT, PHH and MPH/DMA, in the V1 dermatome or on the forearm regarding the side, ipsilateral or contralateral to the capsaicin stimulation (SIDE) or the treatment group, sumatriptan versus placebo (GROUP) (interaction for SIDE*GROUP in RM-ANOVA, p > 0.05 for all QST parameters).

3.2 Changes in warm detection thresholds

After conditioning with capsaicin, WDT decreased (Figure 2) at both test sites (V1 and the forearm) ipsilateral to the application of capsaicin for both the sumatriptan group (V1: −2.1°C, p = 0.008; forearm: −1.6°C, p = 0.001) and the placebo group (V1: −1.8°C, p = 0.005; forearm: −2.5°C, p = 0.006). For contralateral control sites, there was also a trend towards a decrease of WDT in both the sumatriptan group (V1: −0.7°C, p = 0.4; forearm: −0.7°C, p = 0.042) and the placebo group (V1: −0.3°C, p = 0.753; forearm: −0.9°C, p = 0.06). Detailed results of RM-ANOVA regarding the TIME (before and after capsaicin), GROUP (sumatriptan vs. placebo) and SIDE (ipsilateral or contralateral to capsaicin stimulation) for all QST parameters in this study are summarized in Table 1.

3.3 Modulation of primary heat hyperalgesia

After capsaicin conditioning, a marked and significant increase in pain ratings to brief heat stimuli was observed at both test sites (V1 and the forearm) in the sumatriptan group (V1: +35.8/100, p < 0.001; forearm: +38/100, p < 0.001) and in the placebo group (V1: +38.1/100, p < 0.001; forearm: +42.2/100, p < 0.001) ipsilateral to the

![FIGURE 2](image-url) Warm detection threshold changes after capsaicin application. (a) Warm detection thresholds (WDT) at the forehead (V1) and (b) at the arm within the area of capsaicin application (ipsi) as conditioning stimulus and on the non-treated side (contra). White and grey bars indicate the results before and after topical application of capsaicin, respectively. Error bars indicate standard error of the mean. Statistical results of paired t-tests are given. *p < 0.05, **p < 0.01, ns: not significant.
capsaicin application (Figure 3), but no difference has been found on the contralateral control sites in both the sumatriptan group (V1: $-0.38/100, p = 0.872$; forearm: $-1.5/100, p = 0.701$) and the placebo group (V1: $-1.5/100, p = 0.665$; forearm: $+0.2/100, p = 0.957$).

### 3.4 Modulation of secondary mechanical hyperalgesia

MPS directly adjacent to the area of flare induced by capsaicin application increased after capsaicin application at both test sites (V1 and the forearm) in the placebo group, V1 ($\Delta$MPS: $+81.7\%$, $p < 0.001$) and forearm ($\Delta$MPS: $+116.3\%$, $p < 0.001$). In the sumatriptan treatment group, MPS increased after capsaicin application only on the forearm ($\Delta$MPS: $+101.8\%$, $p < 0.001$), but not in the V1 dermatome ($\Delta$MPS: $+12.4\%$, $p = 0.357$), suggesting that sumatriptan attenuated the sensitization of secondary hyperalgesia exclusively in the V1 dermatome (Figure 4). DMA changes after capsaicin application did not differ between the sumatriptan and placebo groups (interaction for TIME*GROUP in RM-ANOVA, $p > 0.05$).

### 3.5 Mapping of the areas of flare and secondary hyperalgesia

Sumatriptan reduced the size of flare after capsaicin application exclusively in the V1 dermatome (sumatriptan vs. placebo group: $923 \text{ mm}^2$ vs. $1213 \text{ mm}^2$, $p = 0.041$; Figure 5), whereas the flare size did not differ on the forearm (sumatriptan vs. placebo group: $2010 \text{ mm}^2$ vs. $1875 \text{ mm}^2$, $p = 0.61$). Sumatriptan did not attenuate the areas of capsaicin-induced secondary mechanical hyperalgesia in either the V1 dermatome or on the forearm.

### TABLE 1

Significant results of repeated-measures analysis of variance (RM-ANOVA)

| Factor       | $F$   | df  | $p$  |
|--------------|-------|-----|------|
| WDT V1       |       |     |      |
| TIME         | 8.209 | 1,38 | 0.007 |
| SIDE         | 6.638 | 1,38 | 0.014 |
| TIME*SIDE    | 8.808 | 1,38 | 0.005 |
| WDT Arm      |       |     |      |
| TIME         | 80.089| 1,38 | <0.001 |
| TIME*SIDE    | 7.075 | 1,38 | 0.011 |
| PHH V1       |       |     |      |
| SIDE         | 204.881| 1,38 | <0.001 |
| TIME         | 12,638,025| 1,38 | <0.001 |
| TIME*SIDE    | 13950.225| 1,38 | <0.001 |
| PHH Arm      |       |     |      |
| SIDE         | 262.957| 1,38 | <0.001 |
| TIME         | 15,523,600| 1,38 | <0.001 |
| TIME*SIDE    | 16,564,900| 1,38 | <0.001 |
| MPS V1       |       |     |      |
| TIME         | 17,499| 1,38 | <0.001 |
| TIME*GROUP   | 7.914 | 1,38 | 0.008 |
| MPS Arm      |       |     |      |
| TIME         | 56.323| 1,38 | <0.001 |

Abbreviations: df, degrees of freedom; MPS, mechanical pain sensitivity; PHH, primary heat hyperalgesia; SIDE, ipsilateral to the application of capsaicin versus contralateral; TIME, before versus after pre-emptive injection of sumatriptan/placebo and conditioning with capsaicin; WDT, warm detection thresholds; V1, forehead.

### FIGURE 3

Primary hyperalgesia after capsaicin application. (a) Pain ratings to heat stimuli ($40^\circ$C) (a) at the forehead (V1) and (b) at the arm within the area of capsaicin application (ipsi) as conditioning stimulus and the non-treated side (contra). White and grey bars indicate the results before and after topical application of capsaicin, respectively. Error bars indicate standard error of the mean. Statistical results of paired $t$-tests are given. ***$p < 0.001$, ns: not significant.
Our data demonstrate that sumatriptan prevents capsaicin-induced secondary mechanical hyperalgesia, but exerts no effect on primary thermal hyperalgesia, suggesting that sumatriptan prevents the central sensitization (of the secondary sensory neurons) without modulating peripheral sensitization. This is in line with earlier studies: in an animal model, intravenous infusion of serotonin effectively inhibits evoked trigeminal nucleus (secondary sensory neurons) firing via its action on the 5HT1B/1D receptor (Goadsby & Hoskin, 1998), and in humans, sumatriptan given early after the onset of migraine can effectively abort the attack and prevent central sensitization. Once central sensitization is established, sumatriptan is less likely to resolve the pain completely (Burstein et al., 2004). Moreover, even though sumatriptan was administrated systemically, we demonstrated that the impedance of central sensitization is trigeminal dermatome specific (V1) but not in an extracephalic dermatome (forearm), echoing the clinical observation that triptans can be used to treat headache (trigeminal dermatome) but not systemic pain disorder (e.g. knee pain).

By showing no effects on primary hyperalgesia but only on secondary hyperalgesia specifically in the trigeminal dermatome, our study provides evidence that a reduction of central sensitization is one important mechanism of how sumatriptan aborts a migraine attack. Notably, capsaicin-induced secondary hyperalgesia was modulated by the second-order wide dynamic range neurons in the spinal cords or in the TNC, not the tertiary sensory neuron in the thalamus (Lee et al., 2007). In human cadavers, 5HT1D receptors within the medulla are located on the fibres (of the primary sensory neuron) but not the cell bodies (of the secondary sensory neuron, i.e. spinal trigeminal nucleus) (Longmore et al., 1997), supporting a more likely site of action in the presynaptic receptors between the gap of the axonal terminals of the peripheral primary sensory neurons and the cell bodies of the secondary sensory neurons. Therefore, in line with the electrophysiological study by Levy et al. using an animal model (Levy et al., 2004), the current study provides functional evidence in humans to support the presynaptic receptors as a plausible site of action for sumatriptan to prevent central sensitization—a possible mechanism in aborting migraine attacks.

Following the previous discussion, we further suspect that the mechanism of how sumatriptan prevents central sensitization is CGRP dependent. CGRP receptors in the dorsal horn are involved in not only the generation but also the maintenance of mechanical allodynia and hyperalgesia (Sun et al., 2003). In an animal model, sumatriptan inhibits the release of CGRP and substance P from the presynaptic terminals of the axons of the primary sensory neurons in the spinal cords (Arvieu et al., 1996); in humans, sumatriptan decreases the plasma CGRP concentration during nitroglycerin-induced migraine attacks (Juhasz et al., 2005). This presynaptic site of action in reducing CGRP release echoes our findings of the
presynaptic site of action in reducing central sensitization. Notably, the distribution of CGRP receptors differs in trigeminal versus extracephalic dermatomes: CGRP receptors are located on the Aδ-fibres and satellite glial cells (Edvinsson et al., 2019; Eftekhari et al., 2010); and the proportion of Aδ-fibres is greater in the trigeminal sensory system—Aδ-fibres account for 50%–60% in the trigeminal sensory roots, compared to 20% in the spinal dorsal roots (DaSilva & DosSantos, 2012). Evidence from fremanezumab, a CGRP-monoclonal antibody (CGRP-mAb), suggests that fremanezumab selectively inhibits Aδ-fibres but not C-fibres in the meninges, further reinforcing the idea of the different roles of different fibre types in trigeminal and somatic nociception (Melo-Carrillo et al., 2017). A recent human study has shown that a single dose of erenumab (a monoclonal antibody against CGRP receptor) suppressed cortical evoked potential when the Aδ-fibres in trigeminal dermatome was stimulated, but not the extracephalic dermatome (de Tommaso et al., 2021), further reinforcing a dermatome-specific mechanism of action. The difference in fibre composition and the involvement of CGRP provides a possible explanation of how sumatriptan preferentially inhibits the induction of secondary hyperalgesia in the trigeminal dermatome but not the extracephalic dermatome.

In the current study, sumatriptan reduced the size of the capsaicin-induced flare. This modulation is exclusively in the trigeminal (V1) dermatome, not in the somatic dermatomes. We suspect that the reduction of the flare is based on a mechanism different from the induction of secondary hyperalgesia. Capsaicin works via its binding to the transient receptor potential vanilloid 1 (TRPV1) (Caterina et al., 1997), and 5-HT receptors can modulate TRPV1 function in animal models (Ohta et al., 2006). Yet, the subtypes of 5-HT receptors that modulate TRPV1 activity seemed different in trigeminal ganglion (TG) and dorsal root ganglion (DRG): in more than 70% of DRG neurons, 5-HT activation potentiated capsaicin-induced TRPV1 responses via the 5-HT2A and 5-HT7 receptors (Ohta et al., 2006); on the contrary, in TG cells, only 5HT1B, 5HT1D, 5HT2A, and 5HT3A mRNA co-localized with TRPV1 (Ohta et al., 2006), and sumatriptan inhibits TRPV-1-mediated currents via its action on the 5-HT1B,1D receptor (Evans et al., 2012). This provides an explanation why the sumatriptan specifically reduced the size of the flare in the trigeminal dermatome. Notably, capsaicin-induced flare is primarily via the axon reflex flare response in the peripheral sensory fibres (Helme & McKernan, 1985). We note that even though primary headache hyperalgesia was not modulated by sumatriptan, we cannot completely exclude a peripheral mechanism of action of sumatriptan. Alternatively, some studies suggested that secondary mechanical hyperalgesia might (partially) contribute to vasodilation that leads to flare (Serra et al., 1998; Sumikura et al., 2003). The slightly decreased flare size may be attributed to the reduced secondary hyperalgesia.

Several limitations must be addressed: (i) the concentration and the duration of stimulation with capsaicin were determined based on the results of our propaedeutic experiments. The differences in the concentration (0.25% in V1 dermatome, 1% on the forearm) and the duration (5 min in V1 dermatome, 20 min on the forearm) render the direct comparison between the trigeminal and extracephalic dermatomes difficult. Similarly, the trigeminal-specific modulatory effect, as we have demonstrated, may also be influenced by the different stimulation protocols of capsaicin. Variability of the structure and reactivity of the neurovascular unit in different body sites is, unfortunately, the inherent limitation of a topical capsaicin model (Helme & McKernan, 1985) (ii) The mechanism of capsaicin-induced peripheral sensitization (and secondary central sensitization) is via the TRPV-1 receptors. Whether this TRPV-1-dependent activation can be translated to spontaneous activation of the primary sensory neurons as seen in patients during their migraine attacks remains unknown. (iii) In addition to the mechanism explored in the current study, brain imaging studies suggested that there may be (additional) central components in clinical response to sumatriptan—sumatriptan, compared to aspirin or placebo, induced stronger activation in the sTN and the thalamus, and altered functional coupling between the sTN and higher brain areas (Kröger & May, 2015); in another non-human primate study, intravenous sumatriptan was associated with minor (6%) central 5-HT1B receptor occupancy in the cortex and cerebellum (Hansen et al., 2017). Therefore, more than one mechanism of action may coexist, and the central effects above the medulla are beyond the scope of the current study. (iv) The sequence of measured sites and the QST parameters were not randomized in the current study. The effect of measuring one parameter (e.g. primary heat hyperalgesia) might influence the following measurement (e.g. MPS). However, both parameters were measured at different skin areas, which renders the possibility relatively low. (v) In the current study, subjects who received sumatriptan, compared to placebo, had reduced MPS, whereas the area of secondary hyperalgesia did not differ. The lack of difference in the area of secondary hyperalgesia may be due to high interpersonal variation. Instead, MPS was compared intrapersonally, before and after capsaicin application. A crossover study design may solve the problem.

5 | CONCLUSIONS

We demonstrated that sumatriptan leads to reduced central sensitization in humans and this reduction is
trigeminal dermatome specific. Our data echo those in the animal model and provide functional evidence in humans that sumatriptan possibly works on the presynaptic receptor between the fibres of the primary sensory neurons and the cell bodies of the secondary sensory neurons. A different composition of sensory fibre subtypes may explain the specific role of the trigeminal system compared to the extracephalic somatosensory system, and why triptans work specifically against trigeminal nociception.

AUTHORS CONTRIBUTION
KP: Data analysis and interpretation, drafting and writing of the manuscript. TJ: Data acquisition, analysis and interpretation, drafting of the study, drafting and writing of the manuscript. HB: Data analysis and interpretation, drafting and writing of the manuscript. LO: Data analysis, data interpretation, and drafting the manuscript. AM: Drafting of the study, data analysis, data interpretation, drafting and revision of the manuscript. All authors discussed the results and commented on the manuscript.

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CONFLICT OF INTEREST
All authors agree with the content of this manuscript. None of the authors have any financial conflict of interest with any content of this manuscript.

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