

Universität Zürich  
Zentrum für Zahnmedizin  
Klinik für Kaufunktionsstörungen und Totalprothetik  
Direktor a.i.: Prof. Dr. sc. tech. Luigi M. Gallo

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Arbeit unter der Leitung von PD Dr. med. Dr. med. dent. Dominik Ettl

**Tracking local anesthetic effects using  
a novel perceptual reference approach**

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## Tracking local anesthetic effects using a novel perceptual reference approach

Dominik A. Ettlin,<sup>1\*</sup> Nenad Lukic,<sup>1\*</sup> Jetmir Abazi,<sup>1</sup> Sonja Widmayer,<sup>3</sup> and Michael L. Meier<sup>1,2</sup><sup>1</sup>Center of Dental Medicine, University of Zurich, Zurich, Switzerland; <sup>2</sup>Balgrist University Hospital, Zurich, Switzerland; and <sup>3</sup>Department of Psychiatry, Universitäre Psychiatrische Kliniken, University of Basel, Basel, Switzerland

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**Ettlin DA, Lukic N, Abazi J, Widmayer S, Meier ML.** Tracking local anesthetic effects using a novel perceptual reference approach. *J Neurophysiol* 115: 1730–1734, 2016. First published January 20, 2016; doi:10.1152/jn.00917.2015.—Drug effects of loco-regional anesthetics are commonly measured by unidimensional pain rating scales. These scales require subjects to transform their perceptual correlates of stimulus intensities onto a visual, verbal, or numerical construct that uses a unitless cognitive reference frame. The conceptual understanding and execution of this magnitude estimation task may vary among individuals and populations. To circumvent inherent shortcomings of conventional experimental pain scales, this study used a novel perceptual reference approach to track subjective sensory perceptions during onset of an analgesic nerve block. In 34 male subjects, nociceptive electric stimuli of 1-ms duration were repetitively applied to left (target) and right (reference) mandibular canines every 5 s for 600 s, with a side latency of 1 ms. Stimulus strength to the target canine was programmed to evoke a tolerable pain intensity perception and remained constant at this level throughout the experiment. A dose of 0.6 ml of articaine 4% was submucosally injected at the left mental foramen. Subjects then reported drug effects by adjusting the stimulus strength (in milliamperes) to the reference tooth, so that the perceived intensity in the reference tooth was equi-intense to the target tooth. Pain and stimulus perception offsets were indicated by subjects. Thus, the current approach for matching the sensory experience in one anatomic location after regional anesthesia allows detailed tracking of evolving perceptual changes in another location. This novel perceptual reference approach facilitates direct and accurate quantification of analgesic effects with high temporal resolution. We propose using this method for future experimental investigations of analgesic/anesthetic drug efficacy.

pain; anesthesia; pain assessment; analgesia tests; psychophysics

ADVISED BY HIS PSYCHIATRIST friend Sigmund Freud (1856–1939), the Austrian ophthalmologist Carl Koller (1857–1944) successfully performed the first clinical eye operation using cocaine as local anesthesia in 1884 (Ruetsch et al., 2001). Since then, a variety of local anesthetics (LAs) have been brought to market. The comparison between different LAs regarding detailed perceptual changes from the time of injection to complete analgesia remains challenging due to methodological limitations of pain intensity measurement tools. Currently, self-report pain scales are most commonly used for assessing effects of LAs in clinical and research settings (Kambalimath et al., 2013; Kazemeini et al., 2014; List et al., 2006; Meier et al., 2003; Shetty et al., 2015; Zheng et al., 2009). Subjects report pain perceptions by means of visual, verbal, or numeric unidimensional constructs, based on prior

individual pain experiences. Widely used examples are visual analog scales (VAS), verbal rating scales, numerical rating scales (NRS), and faces pain scales-revised (Ferreira-Valente et al., 2011; Hjermstad et al., 2011; Jensen et al., 1998). Some studies in the dental field recorded analgesic levels minute by minute on a VAS during application of noxious electric dental pulp stimulation (Batista da Silva et al., 2010; Certosimo and Archer, 1996; Daubländer et al., 2012; Kämmerer et al., 2012; Moore et al., 2006). A shortcoming of these scales is the need to transform subjective pain perceptions onto an objective visual, verbal, or numeric construct. The conceptual understanding and execution of this magnitude estimation task may differ among individuals and cultures. Also, subjects can report perceptual changes only within the painful range. An alternative electric stimulation tool is the Painmatcher (Lundeberg et al., 2001). This instrument serves as a perceptual matching device by producing ascending pain stimuli that patients can compare to their own physical pain (Käll et al., 2008). The intensifying of stimulation results from a successively increasing preprogrammed pulse width. Therefore, its use is optimized for clinical rather than experimental investigations, as it does not allow subject-controlled upregulation and downregulation of stimulus strength. New methods capable of capturing progressive analgesic onset in the range of seconds with objective physical units would enhance our understanding of perceptual changes induced by LAs. Therefore, the aim of this study was to use a novel perceptual reference approach to track dental LA effects with high temporal resolution. Its underlying psychophysical concept requires subjects to self-adjust the stimulus strength to a nonanesthetized tooth every 5 s, so that it matches the perceived intensity in an homologous tooth that received a LA injection, while perpetually stimulated with a given stimulus strength. Since electric tooth stimulation evokes reliable and stable pain perceptions (Brügger et al., 2012; Meier et al., 2014, 2015), we opted for this experimental model, but the current approach might be applied to other body sites.

## METHODS

The study protocol, procedures, and signed consent forms were approved by the local ethics committee (Zurich, Switzerland; KEK-ZH-Nr. 2012-0342). Subjects received 50 CHF/h for participation.

**Subjects.** Forty-one male subjects were recruited by advertisement. Exclusion criteria included systemic disease, history of allergy to the components of the LA solutions, LA in the region less than 2 wk before the experiment, caries, large restorations, periodontal disease, or a history of trauma or sensitivity of mandibular canines. Five subjects had to be excluded because the required experimental pain intensity could not be evoked. Two subjects were excluded due to technical problems with the dental splint, leaving a total sample of 34 subjects included (mean age = 26.64; SD = 6.94).

\* D. A. Ettlin and N. Lukic contributed equally to the paper and are listed in alphabetical order.

Address for reprint requests and other correspondence: M. L. Meier, Center of Dental Medicine, Plattenstrasse 11, 8032 Zurich, Switzerland (e-mail: Michael.meier@uzh.ch).

**Experimental material.** Mandibular splints were fabricated from dental impressions made of Blu-Mousse [Blu-Mousse is a fast-setting vinyl polysiloxane material produced by Parkell (Edgewood, NY)] (Brügger et al., 2012; Meier et al., 2014, 2015). Stainless-steel electrodes were embedded into each splint at the labial and palatal centers of the left and right mandibular canine (Fig. 1). To minimize electrical resistance, a 3-mm round piece of hydrogel (AG 602-6; AMGEL Technologies, Lystrup, Denmark) was placed on each electrode. Care was taken that splints did not evoke pain or discomfort. Electrical stimulation was performed by the portable system Complex Motion (Keller et al., 2002). The presentation software controlled the experimental protocol ([www.neurobs.com/presentation](http://www.neurobs.com/presentation)).

**Local anesthetic.** The canine teeth are innervated by nerve fibers of the most distal portion of the mandibular nerve, which is the mental nerve. For the mental nerve block, a solution of 4% articaine {4-methyl-3-[2-(propylamino)-propionamido]-2-thiophene-carboxylic acid, methyl ester hydrochloride} containing 1:200,000 epinephrine was used (Ultracain D-S Forte), which is currently the most commonly used dental LA in Europe (Cowan, 1977; Snoeck, 2012). Articaine proved to be suitable and safe for procedures requiring a short duration of action in which a fast onset of anesthesia is desired, e.g., dental procedures and ambulatory spinal anesthesia, in normal and in special populations (Snoeck, 2012). Similar to other local anesthetics, articaine blocks nociceptive input by reversibly binding to the  $\alpha$ -subunit of the voltage-gated sodium channels within the inner cavity of the nerve, which results in a state-dependent reduction of sodium influx (Becker and Reed, 2012; Wang et al., 2009). The diameter of the nerve determines the degree of neuronal block so that larger-diameter touch, pressure, and motor fibers require higher concentrations of LA compared with small myelinated fibers (pain afferents) (Buckemaier and Bleckner, 2005). Pulp analgesia lasts for 1 to 2 h.

**Psychophysical testing.** The psychophysical testing using the perceptual reference approach consisted of three stages. First, subjects were seated in a dental chair, and individual thresholds for sensory detection (SDT), pain detection (PDT), and experimental pain intensity (EPI; see below) were determined by applying an ascending method of limits. Both left (target) and right (reference) mandibular canines were electrically stimulated with increasing stimulus strength at randomized intervals between 4 and 7 s. Subjects were asked to indicate their first sensory percept (sensory detection threshold, SDT), and their first painful sensation (pain detection threshold, PDT) by lifting their right hand. SDT and PDT were measured three times for each canine. The EPI was determined by further increasing the stimulus strength to both canines until the participant rated a “5” on an 11-point NRS with endpoints “no pain” and “worst pain imaginable.”

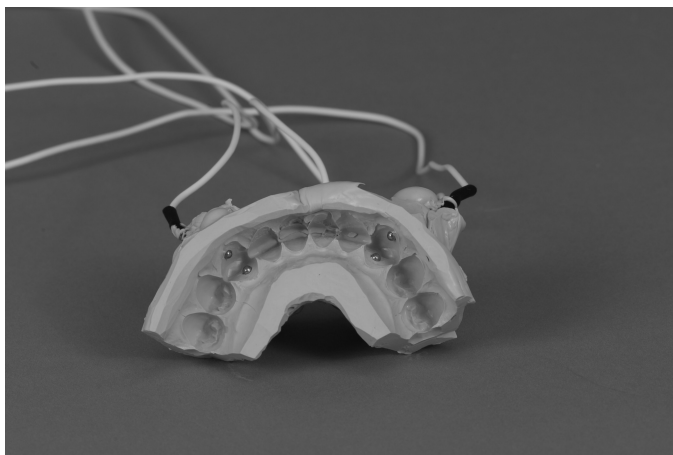


Fig. 1. Mandibular splints fabricated from dental impressions made of Blu-Mousse. Stainless-steel electrodes were embedded into each splint at the labial and palatal centers of the left and right mandibular canine.

The EPI was assessed only once to avoid sensitization/habituation. Additionally, pain quality was assessed by using the three verbal descriptors “pricking,” “dull,” and “pressing.” According to Beissner et al. (Beissner et al., 2010), these three descriptors can be used as a quick discrimination test between A- $\delta$ - and C-fiber-mediated pain.

Next, 0.6 ml of the anesthetic articaine 4% was submucosally injected at the left mental foramen by a single trained dentist (J. Abazi). In nearly closed mouth position, the cheek was retracted buccally away from the premolar area. After palpation of the mental foramen, the needle was inserted submucosally at a 45° angle to the buccal plate and was advanced until bone contact was established at the distal foraminal portion. The needle was then retracted ~1–2 mm, and after aspiration (to avoid injection into nearby blood vessels), the solution was deposited within 10 s.

Subsequently, repetitive electric stimuli of 1-ms duration with the predetermined stimulus strength for evoking the individual EPI were applied first to target mandibular canine (SS-T) and then with a latency of 1 ms to the homologous contralateral reference tooth (SS-R) every 5 s for 600 s. For reporting drug effects, subjects adjusted the SS-R in 1-mA-steps every 5 s. In this way, the perceived intensity was matched to the target tooth (equi-intensity reporting). In addition, subjects were asked to report pain (analgesia) and stimulus offset (complete anesthesia).

## RESULTS

All subjects reported perception of the sensation in the stimulated teeth alone and not in adjacent teeth or tissues. Pain quality was described as pricking by all participants, indicating A- $\delta$ -fiber-mediated pain.

SDTs for target and reference tooth (SS-T: mean = 1.43 mA, SD = 0.79; SS-R: mean = 1.57 mA, SD = 1.27) prior to the equi-intensity reporting did not differ significantly as revealed by a paired *t*-test ( $t = -0.55$ ,  $P = 0.58$ ). Similarly, the analysis of the PDTs yielded no significant difference between both canines (SS-T: mean = 5.20 mA, SD = 2.87; SS-R: mean = 5.70 mA, SD = 3.24;  $t = -0.77$ ,  $P = 0.45$ ). Further, to reach EPI, mean SS-T was 14.29 mA (SD = 6.20) and 15.08 mA (SD = 5.83) for mean SS-R. The corresponding paired *t*-test revealed no significant difference between the stimulation sites regarding EPI stimulus strength ( $t = -0.65$ ,  $P = 0.52$ ).

Figure 2 illustrates the main study outcome: the anesthetized target tooth was continuously stimulated with the stable current strength for evoking EPI (black line). The gray line represents the subject’s perceived intensity in the anesthetized tooth, expressed as subject-adjusted stimulus strength to the reference tooth. After injection, a rapid decrease of SS-R could be observed (slope  $m = -0.20$ ). Time to analgesia was reported after a mean time of 183.08 s (SD = 120.88), with an adjusted mean reduction of 7.11 mA (SD = 2.22) in SS-R, reflecting the analgesic effect.

All subjects achieved analgesia. However, within the experimental time window of 600 s, no complete anesthesia was reached in any of the subjects, depicted by a plateau above 0 mA.

## DISCUSSION

The main finding of this study was that evolving perceptual changes in an anesthetized target tooth could be quantified in detail by subject-controlled matching of the stimulus strength applied to a homologous reference tooth. This novel perceptual reference approach facilitates tracking of LA effects with high temporal resolution, and scores can be treated as ratio data.

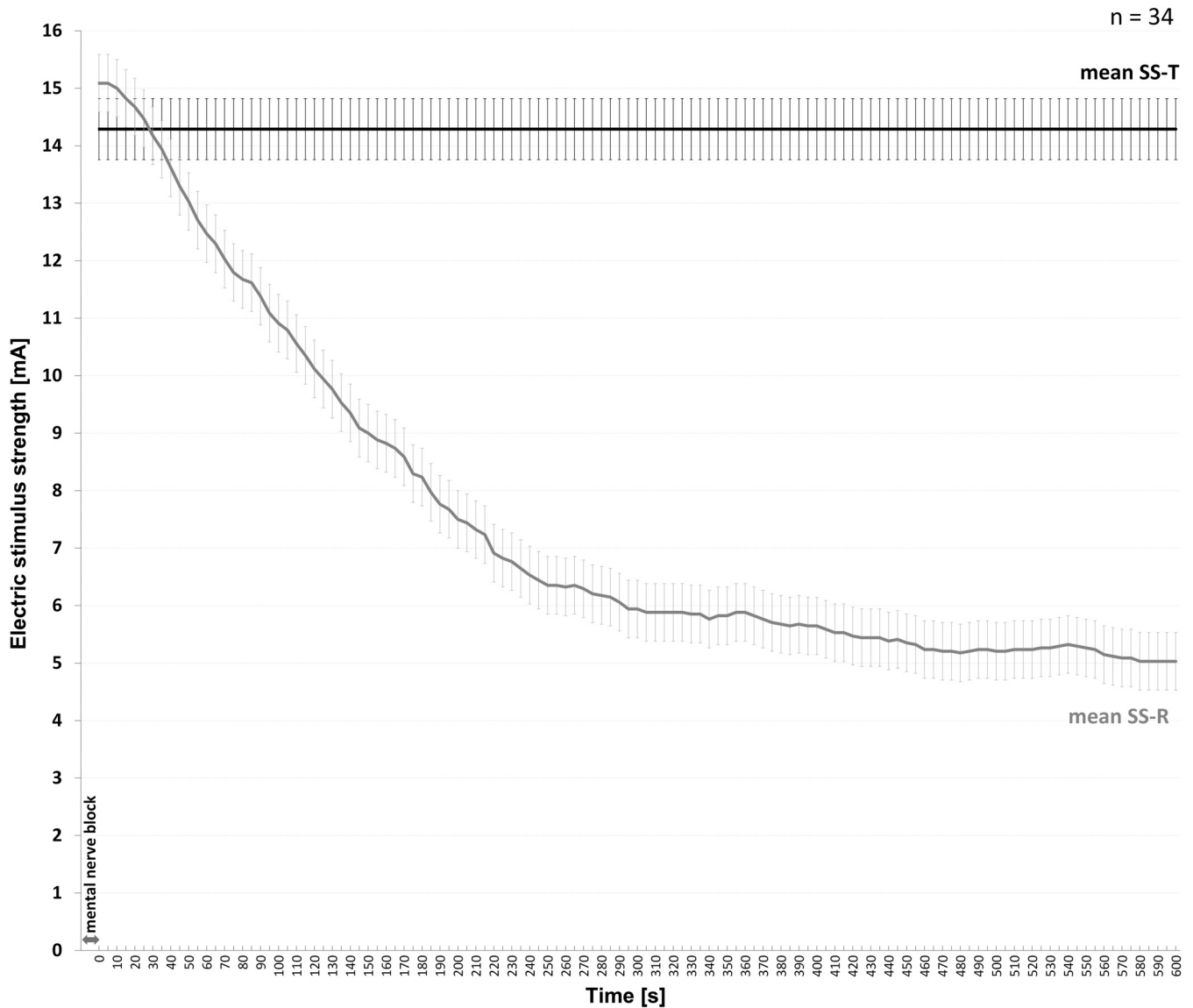


Fig. 2. Equi-intensity reporting: group means ( $n = 34$ ) of the electric current strengths (mA, y-axis) after mental nerve block. The black line represents the constant stimulus strength applied to the anesthetized target tooth (mean SS-T). The gray line represents the subject perceived intensity in the anesthetized tooth, expressed as subject-adjusted stimulus strength to the reference tooth (mean SS-R). The vertical discrepancy between the two lines is a quantitative measure for the analgesic effect. T-bars represent standard error of the mean.

Ernst Heinrich Weber (1795–1878) and his scholar Gustav Theodor Fechner (1801–1887) pioneered the science of psychophysics. Weber introduced the concept of the “barely noticeable difference” between two similar stimuli, and Fechner formulated an equation to express Weber’s theory of the just noticeable difference, also known as the Weber-Fechner law, yielding a logarithmic scale (Fechner, 1860). In many cases, Weber-Fechner’s law is a reasonable fit for magnitude estimation data, e.g., brightness or loudness (Haberich and Lingelbach, 1980; Johnson et al., 1993). However, pain is an exception to Weber-Fechner’s law, as the pain perception rises in an exponential manner with stimulus strength (Nielsen et al., 2005). Nevertheless, our experimental method was inspired by the conceptual framework of Weber and Fechner in the sense that we asked subjects to report barely noticeable differences of stimulus perception in an anesthetized tooth by self-adjusting the stimulus strength to a homologous reference tooth every 5

s. In this way, subjects continuously matched the sensory changes in one anatomic location to the perception in the opposite location. Perceived sensory alterations were recorded in milliamperes, thus allowing high-resolution grading. This approach is a further development of the PainMatcher concept, which is limited by preprogrammed ascending stimuli that cannot be actively modified by subjects.

Our approach conceptually resembles the clinical qualitative sensory testing of bilateral body sites, e.g., in the context of assessing nerve dysfunction. For tracking disease progress, the intensity perception of a given stimulus strength is commonly compared between the diseased and contralateral healthy site. In the current study, we applied an analogous approach: We stimulated both teeth at individually predefined noxious stimulus strength (EPI) and modified the pain experience by a loco-regional nerve block. Rather than offering some sort of a conventional pain scale, we asked subjects to level off the

stimulus strength every 5 s, so that an equi-intense perception in the nonaffected contralateral tooth in reference to the target tooth was achieved. This novel perceptual reference approach renders a high temporal resolution and, thus, allows fine-graded characterization of individual analgesic response profiles.

The idea behind selecting a tooth as a target site for evoking a pure pain experience is not new (Chatrian et al., 1975) and relies on the observation that repetitive electric stimuli reliably evoke short and sharp painful sensations (A- $\delta$ -fiber-mediated pain) and no superimposed mechanosensations or thermosensations (Brügger et al., 2011, 2012; Meier et al., 2014, 2015; Närhi et al., 1992). A- $\delta$ - and C-nociceptors dominate intrinsic tooth innervation. While A- $\delta$  axons end mostly in the inner third of the dentinal tubules, C-fibers end mostly in the pulp itself (Fried et al., 2011; Hildebrand et al., 1995). The few A $\beta$ -fibers innervating the tooth pulp are considered mechanoreceptors that subserve nonpainful sensations, such as tingling when the tooth crown is stimulated electrically at liminal current strength (Fried et al., 2011; Virtanen et al., 1987). We used a tool that previously has been shown to clinically differentiate between A- $\delta$  fiber-mediated sensations compared with other fiber types (Beissner et al., 2010). Although types of pain quality were not the focus of the current study, such investigations might provide some potential area for further research.

The canines in the mandible are predestined for an anesthetic intervention, as the mental nerve is readily and reproducibly accessible for LA injections. The results of this study showed a mean duration of 183.08 s to reach analgesia in the target tooth after submucosal injection of 0.6 ml articaine 4% at the mental foramen. This time span is in line with other studies reporting pulpal anesthesia onsets and related intersubject variability (Colombini et al., 2006; Kambalimath et al., 2013; Moore et al., 2006). The finding underscores the good and fast effect of articaine as a common and safe dental LA. Interestingly, all subjects reported complete analgesia, but none reported total anesthesia. In other words, every person reported the perception of a distinct nonpainful sensation beyond the onset of analgesia until the end of the experiment. This is likely due to easier penetration of articaine through the membranes of unmyelinated and thinly myelinated nociceptive fibers (C-fibers and A $\delta$ -fibers) compared with thickly myelinated A $\beta$ -fibers (Buckenmaier and Bleckner, 2005). Accordingly, the gradient of perception in Fig. 2 can be interpreted as a fast decrease of pain by a rapid inhibition of nociceptive fiber activity. The subsequent slow decrease might correspond to an incomplete nerve block of A $\beta$ -fibers, even after 10 min. Consequently the gradient represents probably less as a logarithmic decrease of homogenous fiber activity, but rather a combination of two linear gradients of different nerve fiber populations. These findings are supported by clinical observations during dental extractions since an A $\beta$ -fiber-mediated pressure sensation is often perceived, even when complete analgesia is achieved.

The novel perceptual reference approach offers several advantages over conventional unidimensional pain scales. First, subjects do not need to transform their experienced pain perception onto a cognitive, unitless construct that heavily relies on past pain experiences. Rather, the current approach offers the possibility to continuously match the stimulus

strength to the level of the sensory perception in the anesthetized canine. Such an approach minimizes the confounding influence of cognitive and affective aspects that are highly intertwined with conventional pain scales. Second, the analgesic effect characterized by the fine-graded gradual loss of sensory perception is directly quantifiable by milliamperage readings, thus allowing for detailed comparisons when investigating the efficacy of various anesthetic compounds. Another aspect that is worthwhile mentioning relates to modern neuroimaging of pain. The current analysis of pain- and analgesia-related brain activity is still highly dependent on individual self-reports of pain (Robinson et al., 2013). Accordingly, the validity of pain-related neuroimaging has been established by correlating brain images to self-reports of pain (Brügger et al., 2012; Coghill et al., 2003; Meier et al., 2012; Wager et al., 2013). The current approach holds the potential to newly quantify individual response profiles from pain onset to offset. Experimental results might be used to better identify central mechanisms that correlate to the analgesia-induced gradual loss of perception.

Although sensitization or habituation effects were not relevant for this innovative methodology article, which investigated relative (i.e., comparative) equi-intensity matching, it is worth mentioning as a study limitation that intraindividual short- and long-term reliability of the analgesic response was not addressed. Short-term reliability would require one to investigate habituation/sensitization effects in case efficacies of anesthetic compounds were to be compared. This aspect would be best addressed by applying a series of stimuli without intervention. Yet, our previous electric tooth stimulation studies using 7–12-s intervals did not indicate habituation or sensitization effect (Brügger et al., 2012; Meier et al., 2014, 2015).

There is growing interest in conducting longitudinal pain studies aiming at investigating neural mechanisms underlying pain-reducing interventions. Hence, a great need arises to assess test-retest reliability of changing individual pain experiences. Further studies using our perceptual reference approach are required to disentangle intraindividual differences of the analgesic response across time. Furthermore, the application of a placebo in further studies would allow new opportunities to track and directly quantify placebo analgesia-related effects.

Our experimental approach might be applied to other body sites, e.g., to quantitatively assess LA effects on the volar forearm (Krumova et al., 2012). However, as tooth pain has some peculiarities regarding sensory innervation and related perception, its feasibility on other body parts has to be determined in a further study.

It can be summarized that pain and its modulation is a subjective experience that is difficult to objectively quantify. For experimental investigations, our novel perceptual reference approach provides individual and rapid information with absolute scaling regarding the perceptual changes after a nerve block. It can be used as an independent pain assessment tool to further compare individual response profiles to different LAs.

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## DISCLOSURES

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## AUTHOR CONTRIBUTIONS

Author contributions: D.A.E., N.L., and M.L.M. conception and design of research; D.A.E., N.L., J.A., S.W., and M.L.M. interpreted results of experiments; D.A.E., N.L., and M.L.M. drafted manuscript; D.A.E., N.L., and M.L.M. edited and revised manuscript; D.A.E., N.L., J.A., S.W., and M.L.M. approved final version of manuscript; J.A. and S.W. performed experiments; J.A., S.W., and M.L.M. analyzed data; M.L.M. prepared figures.

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## Begleittext zur Publikation

Schmerz ist eine unangenehme und durch verschiedene Faktoren modulierte Erfahrung. Sie variiert zeitabhängig interindividuell und intraindividuell für verschiedene Schmerzqualitäten und Schmerzstärken. Klinisch stehen verschiedene Messmethoden zur Verfügung um schmerzhaft Reize zu objektivieren. Die gängigste Methode die Schmerzstärke zu quantifizieren ist die Schmerzskala von 0-10. Diese geht davon aus, dass der Patient den aktuellen Schmerz in Bezug setzt zu einem nicht schmerzhaften Zustand „0“ und einem maximalst vorstellbaren, schmerzhaften Zustand „10“. Damit wird aber eine abstrakte Funktion abverlangt, nämlich die Wertung eines Schmerzerlebens und Übertragung auf eine Nummernskala. Diese beinhaltet unter anderem die Frage: „was halte ich in meinem jetzigen Zustand (noch) aus“. Im klinischen Alltag hat sich der Vergleich mit der gesunden, kontralateralen Seite (sozusagen als „0“) als schnelle und einfache Messmethode etabliert. Wir können bei Patienten einen identischen Reiz auf die linke und die rechte Körperseite an derselben Stelle induzieren und können so sensorische Unterschiede erkennen. Dabei empfängt der Patient zwei identische Signale, unabhängig von Qualität und Intensität und bewertet lediglich den Seitenunterschied mit „gleich“, „mehr“ oder „weniger“. Damit entfällt auch die komplexe Translation auf eine numerische Skala.

Auf diesem Prinzip basierend sollte es möglich sein, den Verlust der sensorischen Wahrnehmung nach einer Lokalanästhesie fein abgestuft zu dokumentieren. Nämlich indem auf der einen Körperseite stets dieselbe, vorher individuell definierte Schmerzintensität appliziert wird und dem Proband die Möglichkeit gegeben wird die wahrgenommene Schmerzintensität auf der Gegenseite mit demselben Schmerzreiz anzugleichen. Damit wird die analgetische Wirkung direkt über die fein abgestufte Abnahme der Stromstärke quantifizierbar.

In dieser Arbeit wurde die Wirkung des in der Zahnmedizin etablierten Lokalanästhetikums Articain untersucht. Es wurden 36 männliche Probanden rekrutiert. Für jeden Probanden wurde eine individuelle Tiefziehschiene aus Silikon für die Unterkieferzähne angefertigt. Im Bereich beider Eckzähne wurde bukkal je eine Elektrode eingearbeitet. Über diese wurden elektrische Stimuli appliziert. Zuerst wurden die individuellen Werte für die Schmerzwahrnehmungsschwelle am Experimentalzahn links bestimmt. Diese subjektiv wahrgenommene Schmerzintensität wurde dann vom Probanden am Kontrollzahn rechts manuell möglichst exakt angepasst. Unmittelbar nach der lokalen Injektion von 0.6ml 4% Articain mit 1:200'000 Adrenalinzusatz am linken Foramen mentale wurde die Wahrnehmung der in kurzen Intervallen applizierten elektrischen Reize am Experimentalzahn vom Probanden am Kontrollzahn die Stromstärke manuell angeglichen. Damit ist es erstmals möglich, den Wirkungsverlauf (Abnahme der Sensibilität) während 10 Minuten mit hoher zeitlicher Auflösung zu ermitteln.

Resultat: Die Schwellenmessung zeigte keine signifikanten Unterschiede der erforderlichen Stromstärken im Seitenvergleich. Eine Analgesie war nach 182.1

Sekunden (SD =  $\pm 117.51$  Sekunden) gegeben. Interessanterweise spürten alle Probanden den elektrischen Stimulus auch nach Ablauf der definierten Experimentalzeit. Dies wurde als unvollständige Anästhesie gedeutet. Die Unterlippe war nach 192.6 Sekunden (SD =  $\pm 123.59$  Sekunden) auf Luftstöße nicht mehr empfindlich.

Schlussfolgerung: Die am Foramen mentale applizierte Menge und Konzentration von Articain zeigte eine wirksame Analgesie im Eckzahnbereich. Die für die Analgesie benötigte Zeit ist mit den vorgängigen Studien zur Wirksamkeit von Articain vergleichbar. Die angewandte Anästhesietechnik ist somit ideal für dentale Eingriffe im Bereich der Unterkieferfrontzähne. Diese Studienanordnung zeigt sich für die Beurteilung analgetischer Wirkungen von Anästhetica als geeignet.

### **Beitrag des Autors:**

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