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Is there a relationship between throbbing pain and arterial pulsations?

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Abstract

Pain can have a throbbing quality, especially when it is severe and disabling. It is widely held that this throbbing quality is a primary sensation of one's own arterial pulsations, arising directly from the activation of localized pain-sensory neurons by closely apposed blood vessels. We examined this presumption more closely by simultaneously recording the subjective report of the throbbing rhythm and the arterial pulse in human subjects of either sex with throbbing dental pain – a prevalent condition whose pulsatile quality is widely regarded a primary sensation. Contrary to the generally accepted view, which would predict a direct correspondence between the two, we found that the throbbing rate (44 bpm ± 3 SEM) was much slower than the arterial pulsation rate (73 bpm ± 2 SEM, $p<0.001$), and that the two rhythms exhibited no underlying synchrony. Moreover, the beat-to-beat variation in arterial and throbbing events observed distinct fractal properties, indicating that the physiological mechanisms underlying these rhythmic events are distinct. Confirmation of the generality of this observation in other pain conditions would support an alternative hypothesis, that the throbbing quality is not a primary sensation but rather an emergent property, or perception, whose “pacemaker” lies within the central nervous system. Future studies leading to an improved understanding of the neurobiological basis of clinically relevant pain qualities, such as throbbing, will also enhance our ability to measure and therapeutically target severe and disabling pain.

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Contributions. AFM participated in study design, institutional approval, and collection of primary data. JM participated in data analysis, writing the manuscript, and figure preparation. JLH participated in collecting primary data and assisted in data analysis. JAK participated in study design, biostatistical analysis and writing of the manuscript. MWH participated in study design, collection of primary data, and writing of the manuscript. MD participated in data analysis and writing of the manuscript. AHA participated in the study design, institutional approval, primary data collection, data analysis, writing of the manuscript, and preparation of the figures.

Conflicts of Interest. The authors declare that there are no conflicts of interest with the work presented in this manuscript.

Introduction

The subjective quality of pain is an essential part of the clinical evaluation. These clinically relevant pain qualities, such as throbbing, crushing, lancinating, or aching pain, are critical details of the evaluation because they suggest invaluable, at times life-saving, clues to the underlying disorder (Armstrong et al., 1998, Rosman et al., 1998, Kreiner et al., 2010). Many recent advances have propelled our understanding of the molecular mechanisms underlying the transduction of thermal and chemical stimuli by pain-responsive sensory neurons (Basbaum et al., 2009). However, very little is known about how these neurophysiologic responses initiate the great diversity of clinically relevant subjective qualities (Ma, 2010). A clearer understanding of the neurobiological basis of these clinically relevant pain qualities would not only improve our fundamental knowledge of pain pathophysiology but would also greatly enhance our ability to diagnose, measure, and design new therapies for clinical pain (Backonja and Stacey, 2004, Hansen et al., 2007, Victor et al., 2008, Jensen et al., 2010).

Among the many pain qualities, a throbbing or pulsatile quality is clinically relevant because it accompanies the most severe forms of acute pain (Aslan et al., 2009), correlates with disease severity (Ballard et al., 2010), and signals disease progression, such as the metastatic spread of cancer (Lam and Schmidt, 2011). The experience of throbbing pain also associates strongly with a lack of response to currently available therapies (Burstein et al., 2000, Wallny et al., 2001), greater functional disability (Jensen et al., 2010, Blumenfeld et al., 2011), and comorbid depression (Kolotylo and Broome, 2000). Thus a delineation of the peripheral and central origins of the throbbing quality could provide important insights leading to the development of novel strategies for the relief of clinically significant pain.

The prevailing scientific view is that throbbing is a primary sensation caused by the rhythmic activation of pain-sensory neurons by closely apposed blood vessels. In dentistry, this model plays a key diagnostic role in inferring the viability of dental pulp from the presence of sensitized afferents and blood vessels (Seymour et al., 1983), though evidence for this view remains indirect (Grushka and Sessle, 1984, Hermanstyne et al., 2008, Kreiner et al., 2010).

Recently, we questioned whether the throbbing quality in the case of migraine pain were related to heart rate (Ahn, 2010), challenging – if only indirectly - an important aspect of the long-held presumption that dilation of the cranial arteries underlies the throbbing quality of migraine pain (Graham and Wolff, 1938). However, because the pathophysiology of migraine pain is still controversial (Strassman and Levy, 2006, Olesen et al., 2009), the ability to generalize to other painful conditions is uncertain. The present study thus focused on the throbbing quality in dental pain, a condition where the peripheral origin of the pain is indisputable. In addition, by analyzing the simultaneously recorded throbbing pain rhythm and arterial pulse with advanced analytical methods, we were able to obtain greater insight into the mechanisms underlying these complex biological rhythms.

Methods

Subjects

Human subjects of either sex with acute dental pain were recruited from patients of the Student Oral & Maxillofacial Surgery Clinic at the University of Florida College of Dentistry, under a protocol approved by the Institutional Review Board. In the normal course of their evaluation clinic personnel identified patients with acute dental pain who additionally reported a sustained throbbing quality. Study personnel were on hand to obtain informed consent and perform the study in a manner so as to minimize interference with the

usual course of treatment. The inclusion criteria were that subjects are 18 years or older, fluent in English, and have a recent onset of dental pain, within one week of the evaluation. A *post hoc* criterion was that analgesia was achieved after the injection of local anesthetic, which was satisfied in all cases.

Descriptors of dental pain

Subjects rated the overall intensity of their dental pain on a 0-10 scale, with 0 representing no pain and 10 representing the worst imaginable pain. Subjects described the qualities of their pain and confirmed the presence of throbbing pain on a questionnaire containing a column of 21 pain descriptors (Table 1) with a 0-10 scale of relative intensity next to each descriptor. This questionnaire closely follows the short form McGill Pain Questionnaire (SF-MPQ) (Melzack, 1987) with minor modifications intended to more clearly define the temporal characteristics of the pain (items 7-10).

Recording of throbbing rhythm

Simultaneous recording of the throbbing rhythm and arterial pulse were recorded on a BIOPAC MP-150 acquisition device (BIOPAC, Inc, Goleta, CA) at a sampling rate of 1000 Hz. Subjects indicated the rate and timing of the maximal point of pressure of the throbbing experience through the use of a sliding rheostat or push button. A pulse plethysmography probe attached to the earlobe simultaneously monitored the waveform of the subjects' extracranial arterial blood flow. The subjects provided 2-3 min of a simultaneous digital recording of their report of a throbbing rhythm and their arterial pulse. We obtained 48 recordings and analyzed 29 of these records more closely.

Statistical analysis

Arterial pulse and throbbing rates were obtained from representative portions of the record, excluding periods in the record containing interruptions of the task or artifacts in the arterial pulse, which were infrequent. The average rates are presented as the mean beats per minute (bpm) ± standard error of the mean (SEM). The average difference between throbbing and arterial pulse rates was tested versus a null of no difference with a paired Student's t-test, with $p<0.05$ set as the criteria of significance. The Pearson product moment correlation coefficient between the two measured rates was determined with the null hypothesis of unity. We present a 95% confidence interval, noting that the conventional view predicts a high correlation (such as $r>0.85$).

There were 19 records that were excluded from the analysis because they were clearly too slow and/or too irregular to have a plausible relationship to arterial pulse. Specifically, the average throbbing rate from these 19 records (17.2 bpm ± 2.6 SEM) was clearly much slower than their corresponding average heart rates (75.5 bpm ± 2.6 SEM. $P<0.0001$ unpaired t-test), and the standard deviation of the inter-event interval (3.7s ± 0.68) was much larger than those reported by the other subjects included in this study (0.29s ± 0.03, $P<0.0001$ paired t-test). In the post-recording debriefing, all of these subjects indicated a distinct lack of confidence in their report of the timing of their throbbing experiences. This proportion of people with difficulty reporting an internally perceived rhythm is consistent with our separate psychophysical control studies in which we asked normal healthy subjects to report their own arterial pulse, using the same recording apparatus; those who were unable to report their own arterial rhythm similarly recorded slow and non-rhythmic responses. The exclusion of these records from the present analysis did not affect the conclusions of this study. In fact, their inclusion would have further strengthened the numerical differences between the throbbing rhythm and arterial pulse.

Spectral analysis of heart rate and throbbing rate

We investigated the temporal dynamics of throbbing and arterial pulse rhythms using spectral methods. The throbbing and arterial pulse records were filtered through a zero-phase filter set between 0.01 and 100 Hz and downsampled to 200 Hz. We used the midpoint of the rising phase in each cycle to represent discrete throbbing and arterial pulse events. The temporal sequence of discrete events was smoothed by using a Gaussian kernel at full width half maximum (FWHM, equal to the average inter-event interval) We calculated the power spectrum of each smoothed time series using Welch's method, normalized by dividing the total power, and then averaged across all subjects to yield the population power spectrum for throbbing and arterial pulse.

Determination of fractal scaling exponent

We further analyzed the throbbing and heart rate variability by converting the discrete event sequence into an instantaneous rate time series where the instantaneous rate was defined as the inverse of the interval between two adjacent events (Berger et al., 1986, Potter and Kinsner, 2008). We calculated the power spectrum of each instantaneous rate time series, again using Welch's method. For the arterial pulse, this analysis is in agreement with previous fractal analyses of heart rate variability (Kobayashi and Musha, 1982, Komatsu et al., 1997) showing that the power spectra of the instantaneous heart rate time series are well described by a power law ($1/f^{\alpha}$ type), where the fractal scaling exponent α is defined by the slope of the log-log plot in the frequency range between 0.04 and 1Hz. Previous work on changes in heart rate variability after cardiac bypass surgery have hypothesized that changes in the value of α represent a change in the autonomic regulation of the heart (Komatsu et al., 1997). To our knowledge the present work is the first study to apply an analogous fractal analysis to the rhythm of throbbing pain. The significance of the difference in α between heart and throbbing rate variability, assessed by a paired t-test, was taken as evidence of distinct mechanisms underlying these two rhythms.

Phase coupling analysis

To address the temporal relationship between the two rhythms, we analyzed the phase synchronization between the heart rate and throbbing rate waveforms. Because the throbbing and heart rates were usually different ($f_{HR} \neq f_{throbbing}$), we applied a method that can examine phase relationships between two non-identical oscillators synchronized at a m:n frequency ratio (Tass et al., 1998). Let the relative phase between the two oscillators be, $\psi_{n,m}(t)=n\phi_1(t)-m\phi_2(t)$, where ϕ_1 is the phase for heart rate, and ϕ_2 is the phase for throbbing rate at time t determined by the Hilbert transform. Here m and n are integers so that m/n is close to $f_{HR}/f_{throbbing}$. For example, if the total event number of heart beat and throbbing is 75 and 65, then we used both 7/6 and 8/7 as m/n for the tests. If the two oscillatory activities are independent then the distribution of $\psi_{n,m}(t)$ is uniform. A departure from uniform distribution gives evidence for coupling between the two oscillators. We assessed the uniformity of the relative phase distribution using Kuiper's test (Fisher 1995). If the Kuiper statistic V is larger than 1.62 ($p<0.1$) then the distribution is considered non-uniform. Setting even this lenient criterion none of the subject records (including the 19 records that were set aside from the main analysis) showed evidence of phase coupling.

Results

At a university-based student oral surgery clinic, in the normal course of 512 evaluations, clinic staff identified 48 subjects who reported a strong and distinct sense of throbbing pain. Of these, 29 subjects were able to record a throbbing pain whose rhythm could possibly be related to their arterial pulse (see Methods).

Overall pain characteristics

Subjects were on average 36 years old ± 2 SEM, and were 66% women. They reported moderately high pain intensity, averaging 7.7 ± 0.4 SEM on a scale from 0 to 10 (see Methods). In addition, the subjective qualities of their dental pain, described by ratings of words from a questionnaire with 21 pain descriptors (Table 1; Figure 1A), had characteristic features. The qualities of throbbing (descriptor #8), aching (descriptor #1) and tender (descriptor # 16) were prominent, and were similar to the responses from an unselected sample of 51 consecutive patients obtained on alternate clinic days. This unselected sample also resembled the overall characteristics of the subject group, being on average 37 years old ± 2 SEM, 55% women, and also reported moderate to high pain intensity levels (7.2 ± 0.3 SEM).

Throbbing rate and arterial pulse rate

To obtain a psychophysical record, subjects signaled the rhythm and timing of their throbbing experience by pressing a button connected to a digital recording device, while simultaneously recording their arterial pulse for 2-3 min. Overall temporal characteristics of the throbbing rhythms included an average throbbing rate (44 bpm ± 3 SEM) that was distinctly slower than the average heart rate (73 bpm ± 2 SEM, $p<0.001$). On an individual basis, the paired throbbing and arterial pulse rates (Figure 1B) were numerically independent (best fit in blue; Pearson $r=0.10$ with 95% CI from -0.28 to 0.45) and inconsistent with the values that would have been predicted by the traditional view (the identity line in red - Figure 1B). Whereas arterial pulse rates respected the usual physiological range, throbbing rates ranged widely, with the most highly represented throbbing rates at 31-40 bpm (Figure 1C).

Spectral analysis of throbbing rhythms

Next we compared the spectral characteristics of each rhythm. Figure 2 shows representative segments of the analyzed waveforms of arterial pulse and the throbbing rhythm from two subjects, one in whom the two rates match closely (Figure 2A) and one in whom the arterial pulse rate and throbbing rate ratio was approximately 3:2 (Figure 2B). The averaged power spectra for all 29 subjects for the arterial blood flow and throbbing experience (Figure 2C) demonstrated the incongruous relationship between these two rhythmic events.

Heart rate and throbbing rate variability observe distinct power laws

We previously noted that for migraine pain the physiologic variation in heart rate (related to respiration) allowed us to observe a clear mismatch between the two rhythms (Ahn, 2010). To address this relationship more systematically, we compared the variability in the arterial and throbbing records, through a spectral analysis of heart rate and throbbing rate variability.

To analyze beat-to-beat variability, we first converted the smoothed waveforms of each record into an instantaneous rate time series (Figures 3A and B), and plotted the averaged power spectra for the instantaneous rate time series for all subjects on a log-log scale, for arterial pulse (HRV) and throbbing rhythm (TRV), respectively (Figures 3C and D). The linear region over the low frequency range indicated the presence of a $1/f^{\alpha}$ power law relationship, as has been previously reported for heart rate variability (Kobayashi and Musha, 1982, Komatsu et al., 1997). As was the case for heart rate variability, the power spectra of the throbbing rate time series were also well described by a power law. However, the fractal-scaling exponent α, which correspond to the average slopes of the log-log plots, are significantly different (1.06 ± 0.10 SEM for heart rate variability and 1.59 ± 0.09 SEM and for throbbing rate variability, paired t-test $p<0.0001$), providing strong evidence that the variability in these rhythms arise from distinct physiological mechanisms.

Phase coupling analysis

Another independent way to appreciate a relationship between two rhythms is to treat each as an oscillator and determine whether there is a relationship (synchrony) between the two oscillators. For a given pair of heart rate and throbbing rate oscillators whose rates had a ratio of m:n the relative phase can be calculated as, $\psi_{n,m}(t)=n\phi_1(t)-m\phi_2(t)$, where ϕ_1 is the phase for heart rate, and ϕ_2 is the phase for throbbing at time t. Figure 4A shows the relative phase distribution for a typical subject where the Kuiper statistic V=0.27 (p>0.1), falls far short of a minimal threshold value of V=1.62 (p=0.1) indicating that the distribution is uniform and that the two oscillators are not coupled. Figure 4B shows the Kuiper's statistic (V) for all subjects, which demonstrates that none of the individual records showed evidence for coupling between the two rhythms.

Discussion

The experience of throbbing pain is prevalent and clinically relevant but poorly understood. Its pulsatile character compels the common presumption that it is in some way linked to heart rate. Some clinical conditions that involve vascular pathology, such as cerebral sinus thrombosis (Wasay et al., 2010), sickle cell crisis (Ballas and Delengowski, 1993), giant cell arteritis (Rozen, 2010), and spontaneous cervical artery dissection (Arnold et al., 2006), have characteristic throbbing qualities that would appear to implicate the experience of vascular dilation, though only indirectly.

Vascular sensations are also a key feature of the current view of migraine (Olesen et al., 2009), a highly prevalent headache disorder whose throbbing quality (Scher et al., 1998, Kelman, 2006) is a diagnostic hallmark (IHS, 2004) and is associated with high severity, frequency, and disability (Blumenfeld et al., 2011). Early studies of migraine focused on the amplitude of cranial artery pulsations, leading to the so-called vascular theory, which hypothesized that the pain of migraine is a primary disorder of cranial artery dilation (Graham and Wolff, 1938). However, several important inconsistencies with the clinical condition draw strong criticism against this theory (Goadsby, 2009). Moreover, data showing a direct relationship between vascular pulsations and the subjects' perception of throbbing remain elusive. More recent electrophysiological evidence for this traditional view, which in physiological terms predicts that pain-sensory neurons are activated by the dilation of blood vessels by normal arterial pulsations, suggest otherwise (Malliani and Pagani, 1976, Goder et al., 1993, Strassman et al., 1996, Levy et al., 2005, Strassman and Levy, 2006).

In more general terms, however, a throbbing quality is common in a broad range of clinical pain conditions involving isolated lesions of the central nervous system, such as in post-stroke central pain (Leijon et al., 1989). In these conditions, the area of brain injury is separated and contralateral to the body region affected by pain, and the abnormal perception of vascular dilation, or any other abnormal peripheral sensory input, would be questionable. Finally, Isnard and colleagues recently reported a patient whose sensory seizures, characterized by throbbing pain, resolved with the ablation of a focal area of cortical dysplasia within the right posterior insula, in the absence of any associated vascular abnormality (Isnard et al., 2011).

The present finding, that the throbbing rhythm exhibits a fractal power law, lays a novel framework for further studies aimed at determining how throbbing pain engages brain regions involved in other important cognitive functions, such as the awareness of pain (Craig, 2009, Lee et al., 2009), or the perception of rhythm and timing (Meck et al., 2008). In addition, because the throbbing quality is associated with a broad range of disabling pain conditions that are refractory to presently available therapies, such as cancer pain (Lam and

Schmidt, 2011), traumatic brain injury (Ofek and Defrin, 2007), sickle cell crisis (Ballas and Delengowski, 1993), pelvic pain (Ballard et al., 2010) and migraine (Blumenfeld et al., 2011), the perception of throbbing pain could possibly serve as a functional target in the development of novel therapeutic approaches for severe and disabling pain.

In addition to the limitations that are inherent to this cross-sectional study, the lack of additional historical detail about our subjects could have adversely affected the results of this study. For example, neuropathic conditions unrelated to dental pulp involvement, such as trigeminal neuralgia, would misrepresent the subject population. However, this clinic by and large provides primary care for patients with dental pain resulting from dental caries, periodontal disease, and trauma. Accordingly, subjects had substantial relief of their pain after the injection of local anesthesia, which assisted in relating the pain to the pulp or associated periodontal tissue. The inclusion of a subject with one of these other conditions would thus be uncommon, and their very infrequent inclusion would not significantly affect the overall conclusions of this study.

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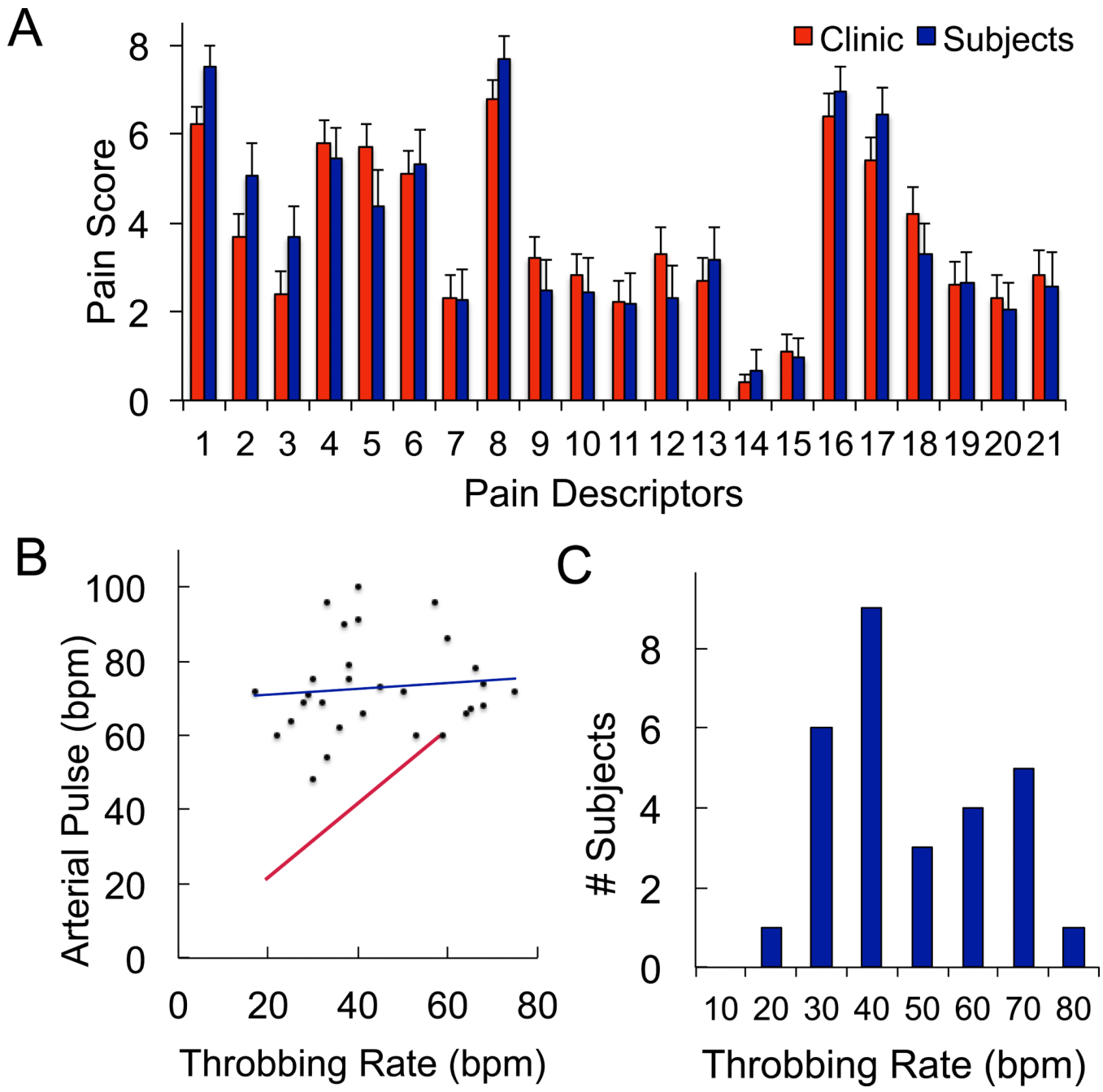

Figure 1.

Throbbing is a characteristic feature of dental pain, and its rate is distinctly slower than heart rate. (A) Subjects (n=29) and an unselected sampling of the general clinic population (Clinic, n=51) confirmed the prevalence of the throbbing quality in dental pain, and demonstrated that the overall pain characteristics of the study sample are similar to the general clinic population. (B) The individual throbbing and arterial pulse rates were unrelated (in blue; Pearson r=0.10 with 95% CI -0.28 to 0.45), and clearly distinct from the prediction by the prevailing view (in red). Overall, the average throbbing rate (44 bpm ± 3 SEM) was distinctly slower than the average arterial pulse rate (73 bpm ± 2 SEM, $p<0.001$).

(C) Throbbing rates ranged widely, but the most common rates were in the range of 31-40 bpm.

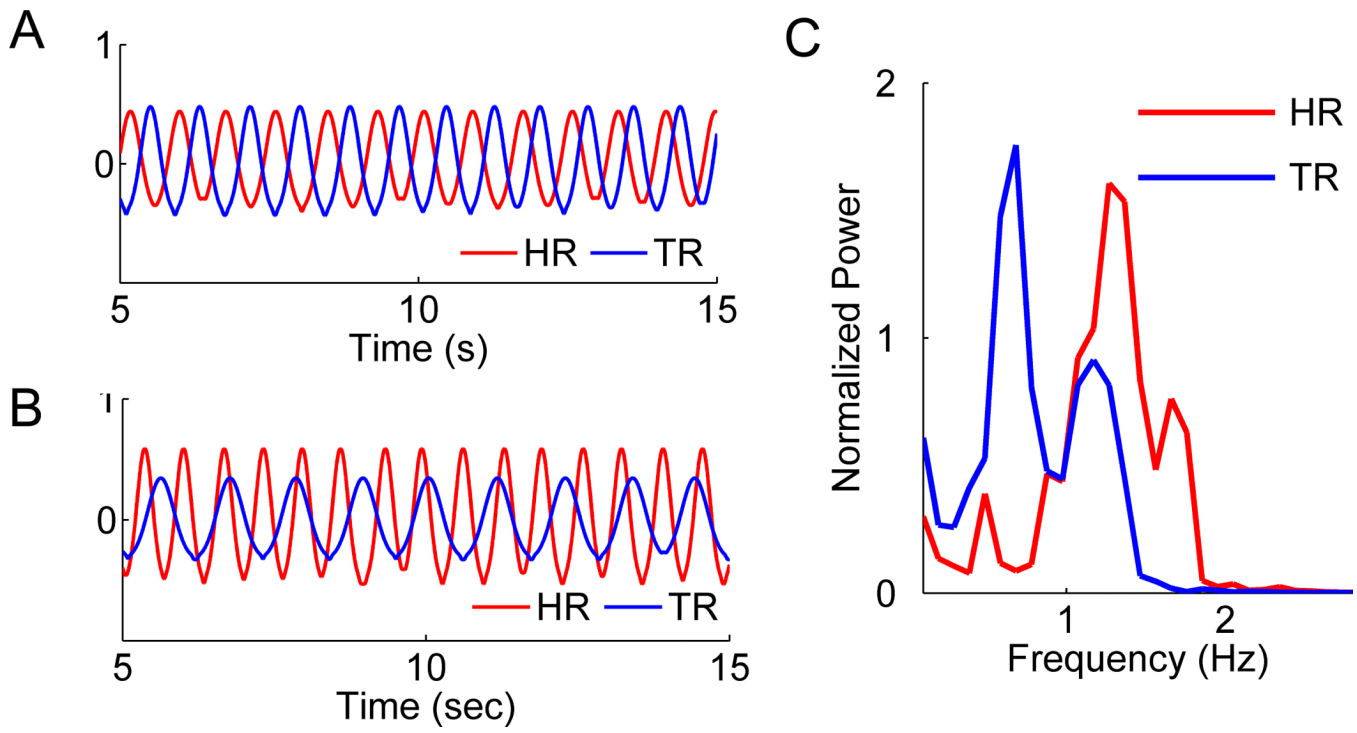

Figure 2.

Spectral analysis of the throbbing rate and the arterial pulse rate reveals their distinct temporal characteristics. The superimposed and smoothed waveforms of the recorded arterial pulse (HR – in red) and throbbing rhythm (TR – in blue) from two representative patients (A) a subject whose frequency ratio $f_{HR}/f_{throbbing}$ is 1:1 (B) another subject whose frequency ratio $f_{HR}/f_{throbbing}$ is 3:2. (C) The average normalized power spectra from all subjects reveals the distinct frequency characteristics of the HR and TR waveforms.

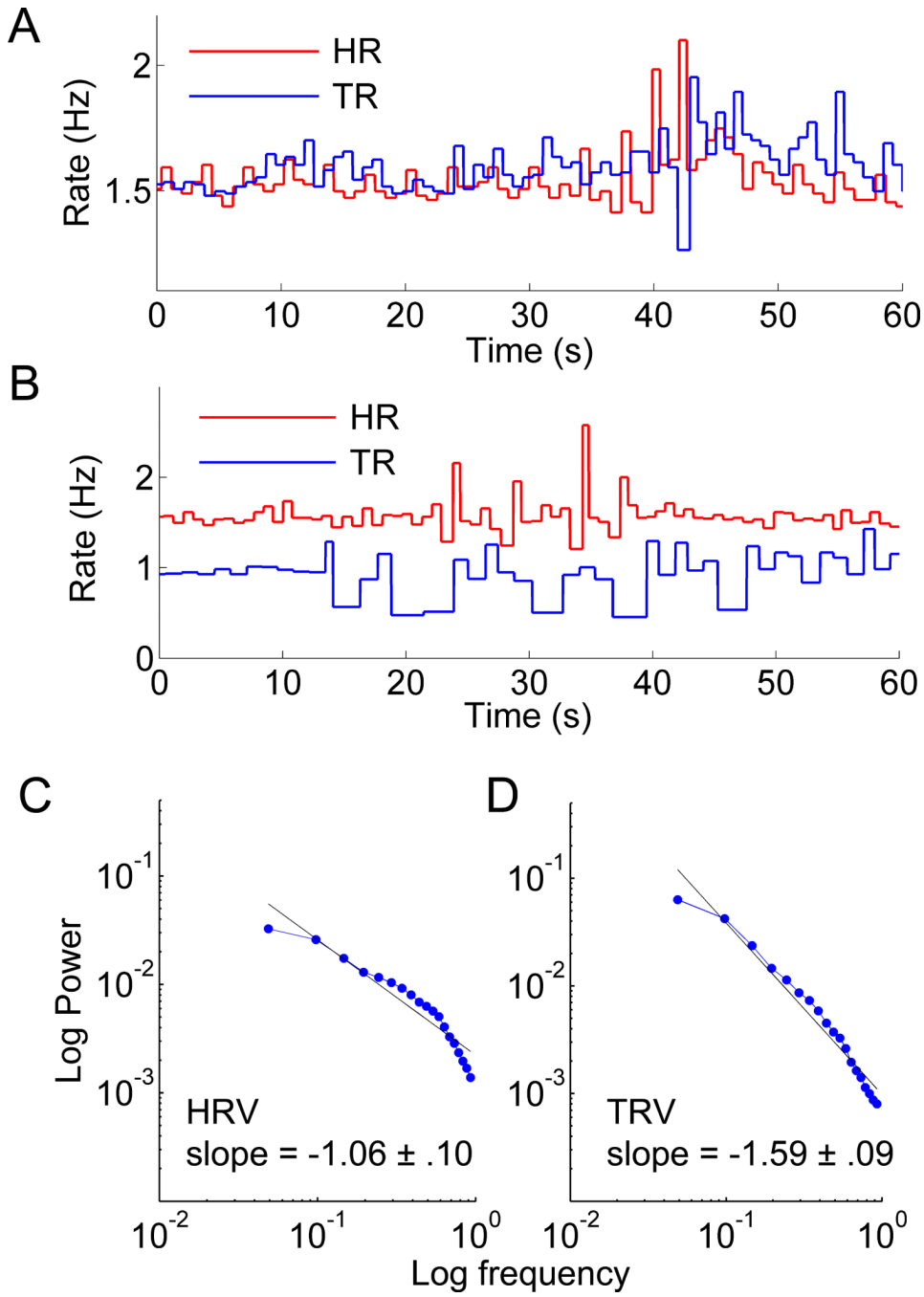

Figure 3.

Fractal analysis of heart rate (HRV) and throbbing rate variability (TRV) shows that the two rhythms observe distinct power laws. Representative instantaneous heart rate (in red) and throbbing rate (in blue) series are shown in (A) and (B) from the same subjects in Figure 2A and 2B. The instantaneous rate was determined by 1/interval between adjacent two events (see Methods). The log-log plots of averaged power spectra of the instantaneous rate series are shown in (C) for heart rate and in (D) for throbbing rate. The black line is the best linear fit. The spectral scaling exponents, defined by the respective slopes (HRV 1.06 ± 0.10; TRV 1.59 ± 0.09), are significantly different (Student's paired t-test $p<0.0001$).

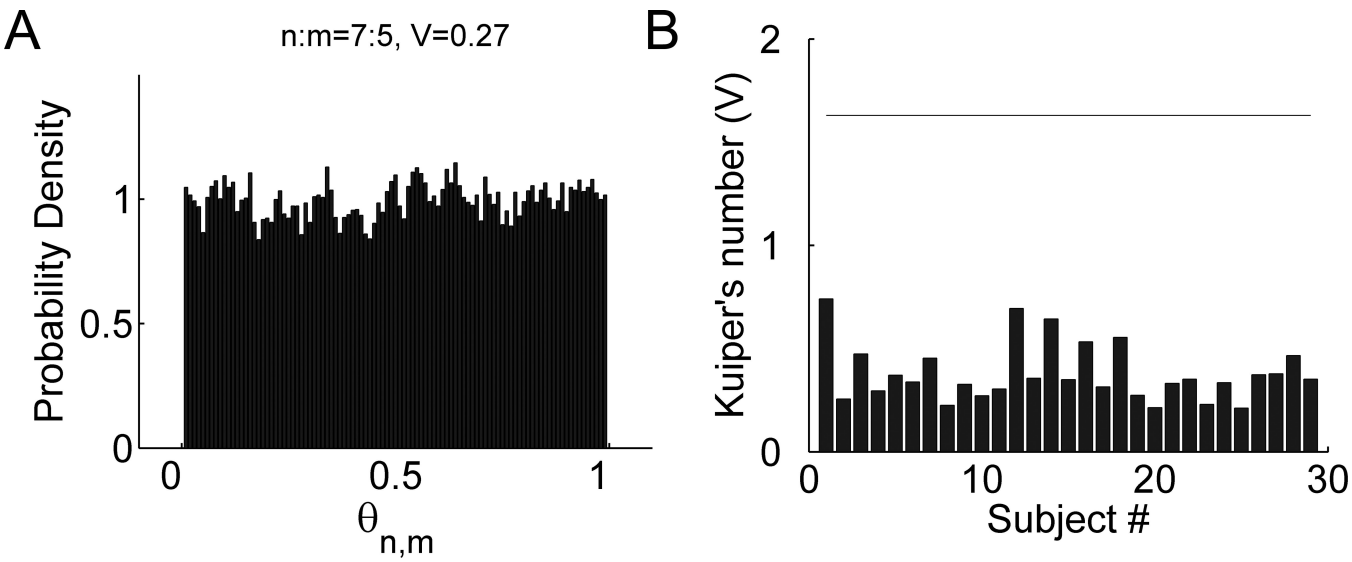

Figure 4.

An analysis of synchrony between arterial pulse and throbbing rhythm shows no relationship. (A) The distribution of the relative phase $\theta_{n,m} = \psi_{n,m} \bmod 2\pi$ in the record from a single subject is approximately uniform, indicating a lack of synchrony. (B) Using a quantitative measure of the uniformity of distribution, the Kuiper's statistic V is below the level of significance for all subjects ($p>0.1$), where the horizontal line signifies $V=1.62$ ($p=0.1$), a minimal threshold for a non-uniform distribution.

Table 1

Pain descriptors used to identify pain qualities. Descriptors highlighted in bold type are those found to be most prominent in this study.

Descriptor Number	Pain Quality
1	**Aching**
2	Heavy
3	Squeezing
4	Sharp
5	Stabbing
6	Shooting
7	Electric-shock
8	**Throbbing, pulsing**
9	Jack-Hammering
10	Exploding
11	Hot-Burning
12	Cold-Freezing
13	Tingling or “Pins and Needles”
14	Itching
15	Numbness
16	**Tender**
17	Pain caused by light touch
18	Tiring-Exhausting
19	Sickening
20	Fearful
21	Punishing-Cruel