Argon laser induced single cortical responses: a new method to quantify pre-pain and pain perceptions

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SUMMARY The shape (amplitude and latency) of single cortical responses to argon laser stimulation was found to match six perceptual classes: three pre-pain and three pain. The amplitude of the pain related single cortical responses correlated with the perceived feeling of pain. Easy detectable responses were obtained because habituation to the stimuli was reduced and a high degree of attention was given to each stimulus. Single cortical responses to argon laser stimuli are suggested as a new quantitative technique with application in the assessment of function in the thermal and nociceptive pathways.

Electrophysiological methods have been used in attempts to measure pain objectively. Percutaneous microneurography1 2 has made it possible to correlate firing rates from single nociceptors to pain perception.

The amplitude of averaged cortical responses evoked by noxious CO₂ laser stimuli are found to correlate with the subjective feeling of pain.3-8 Laser stimuli of identical intensities can be perceived differently9 and the shape (amplitude, duration, latency) of the single responses could therefore be assumed to be different for different perceptions. Conventional averaging does not account for individual differences in the shape of the single cortical responses. We have therefore studied the shape of the single cortical responses in relation to perception.

Laser stimuli of low intensity elicit pre-pain sensations described as throbbing, touching or as warmth. Laser stimuli of higher intensity elicit pain described as stinging, pricking or burning.9 These differences probably arise from activation of different receptors, and changes in firing rates from current activated receptors.

The sensation of warmth has been suggested as conducted by C-fibres with conduction velocities in the range of 0-5 to 2-5 m/s.10 11 The sensation of pricking pain is probably transmitted by Aδ-fibres with conduction velocities between 2 and 30 m/s.12 13

and the sensation of burning pain is assumed to be transmitted by C-fibres with velocities of 0-5-1-5 m/s.14-23

The aim of the present study was to record single cortical responses to non-noxious and noxious argon laser stimulation and relate the shape of single cortical responses to perception and hence the activated fibre population.

Methods

Subjects: Single cortical responses were recorded in 10 healthy young volunteers (six males, mean age 23 years, range 20-31, and four females, mean age 25 years, range 24-28). During the experiment the volunteers were resting comfortably and wore protective goggles. The volunteers were asked to keep their eyes open and fixed on a black spot on the ceiling to minimise slow α-waves and artifacts in the EEG (fig 1). To avoid any acoustic interference synchronised to the stimulus white noise was given through earphones. The skin temperature on the dorsum of the hand was monitored. The room temperature was kept constant (24 ± 2°C) during the experiment. All subjects gave their written consent according to the declaration of Helsinki.

Laser stimulation The output from an argon laser (Lexel Aurora 150, Cooper Medical, USA) was transmitted via a quartz fibre to a handpiece with adjustable beam diameter (0-4 to 6 mm). The laser was operated in TEM₀₀₀ mode. Output power could be adjusted from 0-005 W to 2-9 W. The wave lengths were 0-488 μm (blue) and 0-515 μm (green). An external laser power meter (Ophir, Israel) was used to measure the dissipated output power. A continuous low energy beam (0-005 W) from the argon laser visualised the stimulation site. The stimulus duration was 200 ms and the beam diameter 3 mm. The stimulus was applied to the dorsum (C7 dermatome) of the left hand within a target area

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of 2 × 3 cm². Repeated stimulation at identical spots within
the area was avoided to exclude the effect of receptor fatigue
and receptor sensitisation. The intervals between stimuli
were several minutes because each stimulus had to be
classified and the single responses evaluated.

**Recording of single cortical responses.** The cortical
responses were recorded with a bipolar set of platinum needle
electrodes (Disa 25C04), placed 2 cm behind C₄/C₃

*Fig 1*  EEG signals recorded from one subject (male, 28 years) when the eyes were open (a, b) and fixed on a black spot. Even with open eyes the level of activity varied, and it was therefore of importance to find intervals of low activity when single intervals should be elicited. In c the eyes were closed and slow waves with high amplitude appeared.

(Disa 25C04), placed 2 cm behind C₄/C₃

**Table 1** Scale for the seven subjective ratings and the seven classes of perception to argon laser stimuli (200 ms duration, 3 mm beam diameter).

<table>
<thead>
<tr>
<th>Perceptual Classification</th>
<th>Scale Abbreviation</th>
<th>Class</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very intense pin prick and burning after sensation</td>
<td>VIPP/BS</td>
<td>VIPP + BS</td>
<td>Very strong pain</td>
</tr>
<tr>
<td>Intense pin prick</td>
<td>IPP</td>
<td>IPP</td>
<td>Strong pain</td>
</tr>
<tr>
<td>Sharp distinct pin prick</td>
<td>SDPP</td>
<td>SDPP</td>
<td>Moderate pain</td>
</tr>
<tr>
<td>Distinct pin prick</td>
<td>DPP</td>
<td>Threshold of pain</td>
<td></td>
</tr>
<tr>
<td>Weak or distinct pin prick</td>
<td>PP</td>
<td>Pre-pain/mild pain</td>
<td></td>
</tr>
<tr>
<td>Weak pin prick, warmth</td>
<td>PP/W</td>
<td>WPP + W</td>
<td>Pre-pain</td>
</tr>
<tr>
<td>Weak pin prick followed by warmth</td>
<td>Warmth</td>
<td>Pre-pain</td>
<td></td>
</tr>
<tr>
<td>Painful pin prick, slight touch, faint warmth</td>
<td>1</td>
<td>PP/T/W</td>
<td>Threshold of sensation</td>
</tr>
<tr>
<td>No sensation</td>
<td>0</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

(International 10–20 system) with reference to Fz. The EEG was filtered (0.5–200 Hz) and amplified 200,000 times (Disa 5C01). A microcomputer system was triggered by stimulus onset and 1 second of EEG was collected. The single responses were shown on a monitor and a hard copy was made.

Threshold determination The sensory and pain threshold were defined according to table 1 as subjective rating 1 and 3 respectively. Thresholds were calculated as the mean of five ascending and five descending series of stimulations. Before each experiment the thresholds were determined.

Perceptual classification The volunteers were asked to classify each laser stimulus given according to the classification in table 1. Stimuli not perceived or classified were rejected. The pre-pain and pain stimulus intensity was varied from stimulus to stimulus to obtain responses belonging to all classes. The lowest intensity was below sensory threshold (0.88 ± 0.19 W) and the highest intensity (around 2.00–2.20 W) was well above pain threshold (1.36 ± 0.2 W).

After a response was accepted the classification and corresponding stimulus intensity was noted. After the experiment was terminated the mean laser intensities to each class was calculated. The PP class was a combined pre-pain and pain class and contained both non-painful pin pricks and slightly painful pin pricks. This class was established to reduce the number of classes and make the classification easy for the volunteers and hence more reliable.

Single cortical responses and perception The pre-pain and pain stimuli intensities were varied from stimulus to stimulus to obtain responses belonging to all classes of perception. To each perceptual class a total of three well defined single responses was selected, the perceptual classifications to each response were obtained, and the corresponding laser intensity was noted. Single responses not clearly defined from the ongoing EEG were rejected.
Argon laser induced single cortical responses

Fig 2  Single cortical responses elicited by argon laser stimuli (200 ms duration, 3 mm beam diameter) applied to the dorsum of the hand (male, 29 years). For each class of perception 3 single responses were selected. W and WPP + W are pre-pain responses. PP is a combined pre-pain and mild pain class. SDPP, IPP, and VIPP + BS are related to increased pain.

Fig 3  The amplitudes of single cortical responses for different classes of perception. The 10 columns for each class (hatched) indicate the 10 volunteers investigated. The 3 dots in each column is the amplitude of 3 selected single responses. W is a warmth. WPP + W weak pin prick followed by warmth. PP is a combined pre-pain and mild pain class. SDPP, IPP and VIPP + BS are related to increased pain.
Table 2  The mean amplitude (1/2(\(P_1/N_1 + N_1/P_2\))) and mean latency of the major negative deflection (\(N_1\)) of single cortical responses elicited by argon laser stimuli (200 ms duration, 3 mm beam diameter)

<table>
<thead>
<tr>
<th>Amplitude ((\mu\text{V}))</th>
<th>W</th>
<th>WPP + W</th>
<th>PP</th>
<th>SDPP</th>
<th>IPP</th>
<th>VIPP + BS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency (ms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W</td>
<td>27 ± 9</td>
<td>22 ± 6*</td>
<td>25 ± 7</td>
<td>32 ± 6</td>
<td>41 ± 7</td>
<td>55 ± 9</td>
</tr>
<tr>
<td>710 ± 70</td>
<td>WPP + W</td>
<td>PP</td>
<td>SDPP</td>
<td>IPP</td>
<td>VIPP + BS</td>
<td></td>
</tr>
<tr>
<td>W</td>
<td>442 ± 50*</td>
<td>439 ± 55</td>
<td>421 ± 48</td>
<td>411 ± 41</td>
<td>403 ± 42</td>
<td></td>
</tr>
</tbody>
</table>

The different classes of perception are defined as: W-warmth sensation, PP-weak or distinct pin pricks, SDPP, IPP and VIPP + BS increased pain rating. The mean values (± standard deviation) for each class of perception are calculated on basis of 3 responses from 10 volunteers (mean age 23 years).

Results

Perceptual classification Successive stimuli with fixed intensity could be perceived differently. This was especially marked for stimuli of pre-pain intensity. The pre-pain sensations were elicited by laser intensities below the pain level. When stimuli of fixed intensity were above pain threshold, the elicited sensations were more uniform from stimulus to stimulus and the perceptual classifications remained more stable. The volunteers were able to distinguish between seven classes of perception, no perception, two pure pre-pain, one pre-pain/mild pain and three pure pain classes. If other modalities or sensations were perceived, or if the stimulus could not be classified the stimulus was rejected. The number of stimuli rejected were highest for the pre-pain intensities.

The mean laser intensities were calculated for each perceptual class. No difference was found in intensity between the W, SPP + W classes (0.92 ± 0.32 W, and 1.08 ± 0.30 W respectively), whereas the intensity gradually increased for the PP, SDPP, IPP and VIPP + BS classes (1.29 ± 0.36 W, 1.72 ± 0.29 W, 2.08 ± 0.22 W, 2.48 ± 0.28 W respectively).

Single cortical responses To optimise the conditions for recording of single cortical responses the background EEG was continuously monitored and stimuli were applied when the EEG activity was of low amplitude. In addition the volunteers were asked to keep the eyes open and fixed to avoid slow z-waves and eye movements (fig 1). For each volunteer a total of three detectable single responses were selected for each of the seven perceptual classes. A recording was rejected (1) if the stimulus could not be categorised in one of the existing perceptual classes or (2) if the assumed stimulus related cortical activity could not be detected clearly from the background EEG. Because the pre-pain related single responses were of low amplitude a large number of pre-pain responses were rejected. The large amplitudes of the pain related single responses (fig 2) were obtained because the intervals between stimuli were long (2 to 3 min), and a high degree of attention was given to each stimulus.

Single response amplitude The major stimulus related cortical components (fig 2) could be described by a positive—negative (\(P_1/N_1\)) and negative—positive (\(N_1/P_2\)) deflection. The amplitudes of single responses were estimated as 1/2(\(P_1/N_1 + N_1/P_2\)) and were found to increase (fig 3) for increasing pain rating (PP, SDPP, IPP and VIPP + BS). The mean amplitudes (table 2) of the responses belonging to PP, SDPP, IPP, VIPP + BS increased linearly (\(R = 0.88\)) to the subjective pain rating.

Single response latency The latencies were measured to the major negative deflection (\(N_1\)) and calculated for each class of perception (table 2). The mean latency of the pain related component decreased slightly for increased pain rating (PP, SDPP, IPP, VIPP + BS). The mean latency of the pure warmth related deflection (W) was delayed about 30 ms with respect to the warmth related complex following the pin prick complex (WPP + W).

Discussion

Subjective classification During experiments with CO₂ laser stimulation a certain degree of variability in the perceived sensations were found for fixed levels of sensory input. This variability might be a result of stimulating different receptors and of different receptor densities. Variability in skin constituents, thickness and surface light reflection within the target area might also affect the penetration of laser light and hence the activation of the receptor population. Verbal descriptors of non-painful and painful CO₂ laser stimuli were distributed within three classes: (A) Localised tactile sensations, (B) diffuse tactile sensations, and (C) thermal sensations.

Single responses and perception To low intensity argon laser stimulation three pre-pain classes were established: (1) warmth sensation, (2) touch or non painful pin pricks followed by warmth, and (3) touch or non-painful pin pricks. The single cortical responses could be classified according to perception. The shape (amplitude and latency) showed strong correlation to perception. Conventional averaging of the laser induced pre-pain related single responses did not result in consistent recordings probably because of latency variations. Only when the laser stimuli were reported painful did detectable averaged cortical responses appear. These findings are in accordance with previous results from Carmon et al. Several studies have used the Woody filtering
Argon laser induced single cortical responses
technique of latency correction for waveform esti-
mation of laser induced cortical responses. For pre-
pain stimulation this technique might align warmth
and pin prick related responses, which could lead to
erroneous interpretation of the results.
Averaged cortical responses generated by brief and
intense laser stimuli probably represent a distinct
Aδ-fibre mediated stabbing pain.26 The averaged pain
related responses contains a major complex around
300 to 400 ms,3 8 26 and this complex is found to
correlate strongly with the subjective feeling of pain.
The pain related complex of the single cortical
responses are assumed to be identical to the reported
300–400 ms complex of the averaged cortical
response, because the amplitude of both complexes
are found to correlate with the subjective feeling of
pain.
Warm dolorimeters have been used to evoke
warmth related cortical responses.27 28 Fruhstorfer et
al27 applied warmth pulses on the hand and found
cortical responses with 2 major complexes at
602 ± 191 ms and 771 ± 191 ms. In the present study
warmth related cortical components elicited by low
intensity argon laser stimuli had a mean latency
around 700 ms, which substantiate the validity of the
proposed long latency warmth related cortical com-
ponents.
Even the argon laser intensity increased the
sensation of warmth vanished completely. This might
be explained by two different phenomena: (1)
intracutaneous mechanisms and/or (2) central
mechanisms.
Intracutaneous mechanisms Within the population
of warmth receptors two groups have been identified
in humans. The first has a firing threshold of about
30 °C, with peak firing rates at 40–43 °C. The threshold
for the second group is between 35–38 °C, with peak
firing at or above 45 °C.11 The polymodal nociceptors
are activated by temperatures between 40 °C and
47 °C,22 30 31 with increased firing rate and pain in-
tensity for increased temperature.9 13
Model simulations predict that CO2 laser stimuli
of low intensity provoke only minor and slow increa-
ses of the intracutaneous temperature at receptor
level, even when the surface temperature becomes
relatively high. The slow rise time for the intracuta-
neous temperature is thought to be the same for ab-
sorption of argon laser light of low intensity. The
temperature at receptor level might slowly (fig 4) reach
a temperature of (30 °C) adequate for activation of the
warmth receptor group 1 and warmth receptor group
2 (35–38 °C) without activating the polymodal noci-
ceptors (above 40–47 °C).
When the stimulus intensity increases the intracuta-
neous temperature rises faster and reaches a higher
value.32 If the temperature is just above the nocicep-
tive activation temperature (43–45 °C) slight pin pricks
or other tactile sensations may arise9 dependent of
different firing rates from the receptors. Also, warmth
receptors may be activated when (A) the skin tempe-
rature increases (between 30 and 40°C, on-response)
or (B) when the intracutaneous temperature decreases
(off-response) after activation of the nociceptors (fig 4).
A further increase in laser intensity results in very
fast rise times for the intracutaneous temperature and
the temperature thus passes the range (between 30 and
40°C) for warmth receptor activation very fast and the
on-response sensation might vanish, but the off-response
sensation as the temperature decreases should still be present (fig 4). The averaged latency of
the pure warmth response was slightly longer than the
latency of the warmth response following the tactile
sensation which supports the suggestion that the
warmth sensation arises from the on-response. This
could also explain the disappearance of the warmth
sensation for higher laser intensities.
Central mechanisms In addition to the peripheral
events, central inhibition and processing might
account for interaction between warmth and pain
perceptions, and partly explain the disappearance of
the warmth sensation for higher laser intensities. The
gate control theory33 predicted that activity of large
afferent fibres would produce a presynaptic inhibition
on thin fibres in the dorsal roots. This suggestion
initiated several clinical applications, for example

**Fig 4** The assumed intracutaneous temperature profile at
receptor level. The W1 and W2 lines represent the firing
threshold for the two groups of warmth receptors discovered
by Konietzny and Hensel.11 PP indicate the firing threshold
for the polymodal nociceptors. Argon laser pulses of low
intensity might activate the warmth receptors selectively.
For slightly higher intensities the polymodal nociceptors are
just activated but because of the slow rise time the warmth
receptors can fire for a sufficient length of time to evoke the
sensation of warmth. For strong laser pulses the temperature
rises fast above the noxious level and elicits pain.
transcutaneous nerve stimulation for pain relief.\textsuperscript{34} \textsuperscript{35} Our findings suggest that inhibition of C-fibre mediated warmth by A\textdelta-fibre mediated pricking pain might exist.

\textit{Peripheral conduction velocities} The cortical complexes to pin prick and warmth sensations might be a reflection of central events in the pain and warmth perception process rather than transduction and transmission of the stimulus event. However, the latency difference between the pin prick and the warmth related complexes might represent differences in conduction velocity for the afferent fibre populations activated. Campbell and LaMotte\textsuperscript{36} concluded from reaction time measurements that the afferents transmitting laser induced pricking pain must have conduction velocities greater than 6 m/s. Ultra short laser pulses (0-1 ms) applied to the dorsum of the finger gave reaction times corresponding to 10.2 m/s. If the stimuli pulses were applied to the volar part of the finger the estimated conduction time increased to 15.5 m/s.\textsuperscript{37} The peripheral conduction velocity to laser stimulation has been estimated between 5-8-10-8 m/s on basis of the time delay between pain related cortical responses elicited by stimulations along the arm.\textsuperscript{38} These values are lower than the mean conduction velocity (19.2 ± 7.2 m/s) determined in single A\textdelta-fibres.\textsuperscript{13} If a mean conduction velocity of 10 m/s is assumed for the transmission of pin prick pain and the conduction distance from hand to cortex is roughly estimated to 1 m the pin prick related cortical deflection should appear 100 ms after stimulus onset, without taking the intraneural connections, and the conduction delay for the heat to reach the receptors, into account. The main complex of the single responses appeared after approximately 400 ms (fig 2). The 400 ms correspond then to a mean conduction velocity of 2.5 m/s for 1 m of conduction distance. This conduction velocity is at least 3-4 times lower than expected. The time lag for heat conduction, intraneural transmission times, and a possible central processing may therefore introduce a substantial delay of 200-300 ms. The mean delay between the pin prick related and the warmth related complex are estimated to 250 ms (table 2) the conduction velocity (CV) for the afferent warmth fibres could be calculated as the conduction distance of one meter divided by the assumed latency of 100 ms plus the time interval between the pain related and warmth related complex (250 ms):

\begin{align*}
CV_{\text{warmth}} &= \text{distance (m)/estimated latency(s)} \\
CV_{\text{warmth}} &= 1 \text{ m/(0-250 + 0-100) s = 2-8 m/s}
\end{align*}

which is slightly higher than previous results (0.5 to 2.5 m/s) obtained from microneurographical recordings.\textsuperscript{10} \textsuperscript{11}

In conclusion, single cortical responses elicited by argon laser stimuli are easy to detect and the amplitude correlates with pre-pain and pain perception modalities. Activation of single responses should be exploited in further attempts to study transmission and processing of various perceptual modalities.

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