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Ultra-late EEG potential evoked by preferential activation of unmyelinated tactile afferents in human hairy skin

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Abstract

Human tactile sensibility in hairy skin is mediated not only by fast conducting myelinated ($A\beta$) afferents, but also by a system of slow conducting, unmyelinated afferents that respond preferentially to light touch, C-tactile (CT) afferents. This system has previously been shown to correlate with the pleasantness of tactile stimuli, where a soft brush moving at 1-3 cm/s activates CT afferents strongly. Functional magnetic resonance imaging (fMRI) studies have shown that preferential CT fiber stimulation activates the posterior insula cortex. The present study aims to assess brain activity evoked by the activation of CT afferents using electroencephalography (EEG). We present evidence for a late cortical potential over frontal electrodes, evoked from slow, gentle brush strokes at 3 cm/s. We relate this to the CT afferent input based on the conduction velocity of the CT fibers and the force feedback from the brush; the potential started 0.7 s after the brush contacted the skin and continued throughout the brush stimulation. Furthermore, results from brushing at lower and higher speeds showed that the CT potential was modulated by this stimulation. We conclude that the late potential is consistent with activity in a frontal cortical network following hairy skin peripheral stimulation. This provides an important tool for further studies of the CT fiber system and for clinical examination of peripheral unmyelinated afferents.

Key words: C-tactile fiber, pleasant, stroking, somatosensory cortex, touch

Abbreviations

CT, C-tactile; EEG, electroencephalogram; ERD, event-related desynchronization; ERP, event-related potential; ERS, event-related synchronization; ERSP, event-related spectral perturbation; fMRI, functional magnetic resonance imaging; SI, primary somatosensory cortex.

Introduction

The brain receives signals from many different types of low-threshold mechanoreceptors and their type and density differ depending on the area of skin that is stimulated. In humans, the glabrous skin on the palms contains rapidly-adapting mechanoreceptors (Meissner's corpuscles and Pacinian corpuscles) and slowly-adapting mechanoreceptors (Merkel's disks and Ruffini's endings) [12, 32]. Hairy skin, defined as the non-glabrous and non-mucocutaneous skin covering the majority of the body, does not contain Meissner's corpuscles but instead rapidly-adapting hair and field mechanoafferent units [34]. These afferents have myelinated axons, with conduction velocity in the 37-73 m/s range [16]. In addition, human hairy skin contains a more recently discovered class of unmyelinated low-threshold mechanoafferents, so-called CT afferents [33, 35, 37], with conduction velocity around 0.6-1.2 m/s [33]. CT afferents have so far been found in the face [13, 24], arm [20, 33, 35, 37] and leg [19]. They have small receptive fields, only a few millimeters in diameter, and respond to indentation forces of 250 mg or lower [33, 37]. Microneurography experiments in humans have shown that CT afferent responses can be variable but they fire preferentially to low-velocity (1-3 cm/s) strokes, which correlate with psychophysical measures of pleasantness [20].

In fMRI experiments measuring neural haemodynamic signals, different patterns of activity have been found from touch to hairy skin compared to touch on glabrous skin [25]. Touch that preferentially activates CT afferents sends information to brain areas including the posterior insula, orbitofrontal cortex, prefrontal cortex and cingulate cortex [10, 21, 22, 25, 26, 29]. It is hypothesized that CTs do not project to the primary somatosensory cortex (SI; [25, 26]), where A β afferent tactile information is processed [17, 18]. The increased activity from more frontal areas during preferential CT activation indicates that cognitive and emotional factors co-occur during this type of touch process. This has implications for social touch and affiliative behaviour; decreases in the perception of the pleasantness of touch correlate with decreased brain activations in the insula [22] and also with autistic traits [2, 6, 36].

Studies originating in the field of pain research have previously identified ultra-late components in electroencephalography (EEG), which relate to the activation of C-pain unmyelinated, slowly-conducting afferents [4, 5, 15]. The co-activation of A δ pain afferents can inhibit the detection of the C pain afferent input [4, 5] but techniques such as using selective conduction blocks [4, 5], very small areas of skin [3], sub-threshold stimuli (e.g. heat; [11]) or special analyses [5] can help visualize late EEG components. However, these studies investigate unmyelinated fiber

function using pain; the purpose of the current study was to investigate neural differences occurring through somatosensation on human, hairy skin from non-nociceptive unmyelinated CT fibers. To our knowledge, no previous studies have specifically investigated this comparatively slow touch input to the brain using EEG. We provide evidence to show that an ultra-late potential relating to the CT input can be seen over frontal, midline electrodes.

Material and methods

EEG data were collected from 16 healthy volunteers (aged 19-31, 9 males). Participants were given information about the study, which conformed to local ethical approval and was performed in accordance with the Declaration of Helsinki. Written, informed consent was obtained for all participants and they were paid for participation. The study was carried out using a Biosemi ActiveTwo EEG system (Biosemi, Netherlands) with a 64 electrode cap. Participants were seated with their left arm immobilized comfortably in a vacuum cast. A material screen was placed between the participant's body and their left arm so that they could not see the experiment. The participant was given instructions to attend to the brush stimulus as it moved over their left dorsal forearm. Each experiment consisted of 12 blocks each with 20 brush strokes at 3 cm/s and two 'oddball' strokes at 6 cm/s that were randomly delivered in each block. There was a random pause of 4-6 seconds between the strokes in each block. A total of 240 brush strokes at the required 3 cm/s velocity were acquired. The participant was told to verbally identify oddball strokes when they felt the difference, although they were not aware how many oddballs would occur. They had short rests between blocks. Once the participant was ready to start the experiment, they had earplugs inserted to minimize any noise.

EEG signals were sampled at 512 Hz, using reference-free recordings. The brush strokes were delivered by a custom-built robotic device (rotary tactile stimulator, RTS; Dancer Design, UK) driven by LabVIEW (National Instruments, TX) software. The same robot was used in our earlier psychophysical and microneurographic investigations of the CT afferent system [20]. The brush was a soft, cosmetic brush adapted for the RTS. This enabled highly replicable strokes at speeds of 3 and 6 cm/s in the proximal-to-distal direction along the arm, at a calibrated normal force of 0.2 N. The RTS sent a signal to an EEG trigger channel at the onset of each brush motion. Further experiments were conducted for supplementary information on the time course of the EEG responses to brushing. This was to add evidence towards the timing of any late-onset EEG potentials, which should shift accordingly if the brushing speed was changed. A subset of six participants received additional brush strokes at 2.3 cm/s and 4.5 cm/s, but with slightly

shorter random inter-stimulus intervals, 1-3 seconds. The analysis procedures were the same for these data.

The EEG data were analysed in MATLAB (The Mathworks, MA) using the open-source EEGLAB toolbox [7] with custom-written scripts. The data were imported, down-sampled to 256 Hz and high-pass filtered at 0.1 Hz. Event information from the RTS was imported (an event marker was sent at the onset of RTS movement) and the data were epoched according to this with limits of -1 s to +5 s around the event. The data were re-referenced to an average reference. For each participant, the data were visually inspected and epochs with large artifacts (not eye blinks or eye movements) were removed, as well as the trials at 6 cm/s brushing, which typically also contained noise from verbal identification of the oddballs. There was a high rate of inclusion for the 3 cm/s trials, on average 85% of trials were included from the subjects (range: 67-94% of trials). Independent component analysis [1, 7]) was used for blind-source decomposition of the data into 64 components and the results were used to clean the noise from individual participants' data for event-related potential (ERP) analyses. This algorithm has been shown to be effective in identifying eye movements and blinks [14]. Data from the individual participants were inspected and the data from all the participants were summed in grand-average plots.

Results

The participants were able to discriminate reliably between the 3 cm/s brush strokes and the oddball 6 cm/s strokes. All the participants correctly identified over 99% of the trials, apart from one who had an acceptable pass rate of 86%. The present study focused on the input from the unmyelinated CT fibers, which due to their relatively slow conduction velocity, provided a late somatosensory input to the brain, compared to the faster input from the myelinated A β fibers. We present evidence for the putative response from CT afferents from ERPs. Other, earlier brain potentials were seen in the EEG in response to the brushing from the A β input, but these were not the focus of the present study. These early potential changes (<1s after stimulus onset) were related to the arrival of the fast A β fiber input. However, the potentials seen were not sharp like the somatosensory evoked potentials found typically with electrical nerve stimulation. The ongoing and comparatively slow nature of the stimulus and the small differences in the onset of the brush striking participants' hairs and skin (the event onset was defined as the onset of RTS brush movement), meant the responses were more rounded; we focus on an ultra-late potential that was related to the brush stroking, which we relate to the CT input.

Figure 1 shows the temporal development of the ultra-late, positive potential found over midline, frontal electrodes. The top panel shows the individual responses from each brush stroke, at the maximally responsive location (electrode Fz), although the ultra-late potential was also present at the surrounding electrodes. Responses are sorted by phase at the onset of stimulation. The bottom of the figure shows a topographical overview of the average development of the ultra-late potential over the whole head. From both these plots, it is clear to see the onset of the potential peaked at 2.5 s. Force feedback readings from the brush showed that the total brushing time over the skin was 1.8 s, not including hair stimulation prior to the brush making first contact with the skin. In the figures, 0 s indicates a trigger signal for the time at which the brush started moving; it hit the skin and gave a force feedback on the RTS at typically 0.7 s; calculations from video-based analyses of the brush action found that it first hit hairs on the skin at 0.25 s. The ultra-late, positive potential started at 1.4 s and lasted until 3.1 s, which followed the timing of the brush stimulation with a delay of 0.7 s from the onset of the brush first hitting the skin. This corresponds to delays seen in unmyelinated fibers; the typical length from the skin site on the arm to the vertex was 85 cm, which would give an average conduction velocity of ~ 1.2 m/s for this ultra-late positivity.

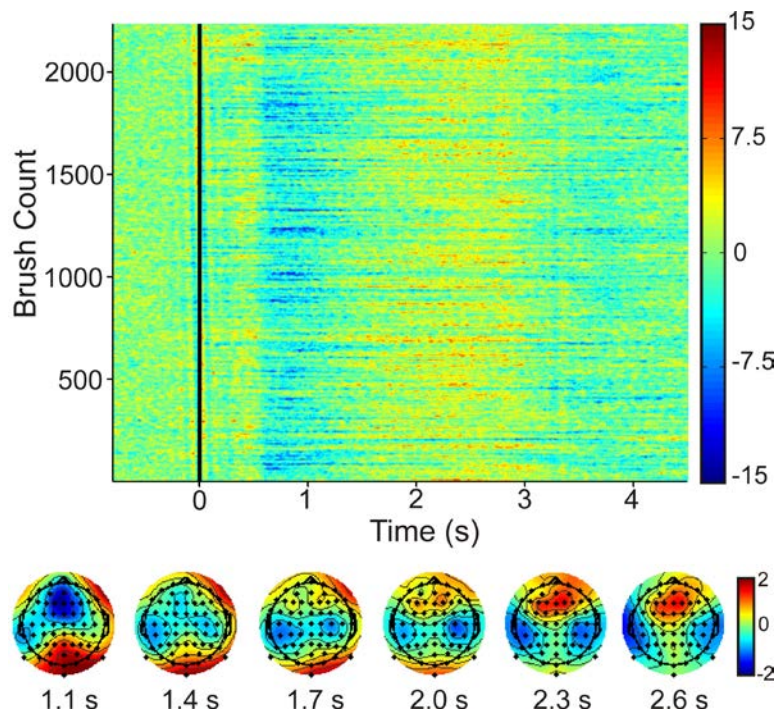


Figure 1: The ultra-late positivity from brushing stimulation, over time. The top plot shows the amplitude responses from all the individual trials from the frontal, midline electrode Fz, sorted by phase at 0 s. The bottom topographical plots show the development of the average ultra-late

response over the head. Both scales in μV , see individual color bars for the scale; from the 11 participants in the main experiment.

To investigate further the timings of the ultra-late potential, we also included a number of experiments with different speeds of brush stroking, namely 2.3, 3 and 4.5 cm/s. This was to see whether the timing of the ultra-late potential was modulated with the change in the somatosensory input. Figure 2 shows the results: the ultra-late potential was shifted in accordance with the different somatosensory brushing speeds. The average time-shift from the force trajectory records to the Fz ERP wave, calculated from the peak in the cross-correlation, was also 0.7 s for all three brush velocities.

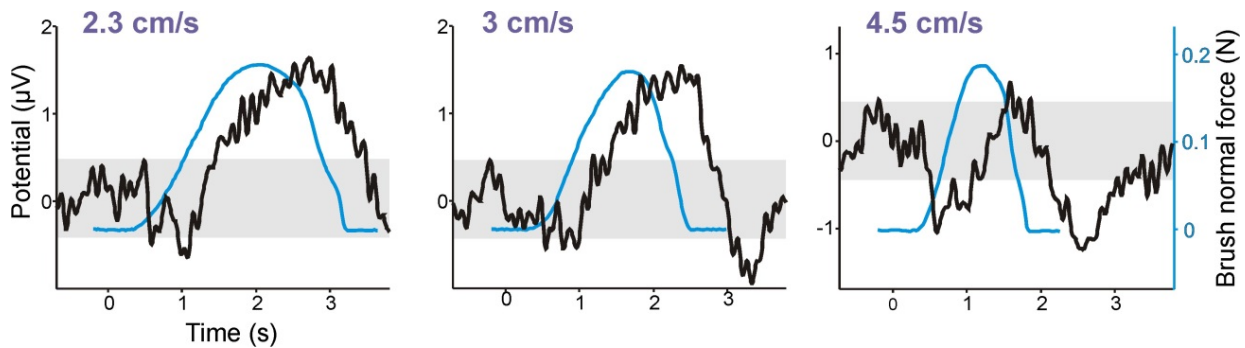


Figure 2: The ultra-late potential varied with the speed of the brush stroke (2.3, 3 and 4.5 cm/s). The black line shows the ERP responses over time and the blue line represents the feedback of the normal brush force over the skin. The gray boxes indicate $p < 0.05$ confidence intervals. Averaged data from electrode Fz in the sub-set of six participants; note, negative potentials are down.

The ultra-late potential was studied in the frequency domain and compared to electrode CP4 (located over the right sensorimotor cortex, contralateral to the brush site). Event-related spectral perturbation (ERSP) data are shown in Figure 3; in comparing these electrodes, the EEG potentials and frequency responses were very different. The positive, early somatosensory potential generated in electrode CP4 had a very different neuronal time course compared to the ultra-late potential, and we relate it to the input from the $A\beta$ afferents. Furthermore, the responses in the ERSPs were different: the data from frontal electrode Fz showed a modulation in the theta (continued synchronization at 6 Hz), alpha (continued desynchronization at 8-10 Hz) and beta (transient synchronization at 13-16 Hz) bands.

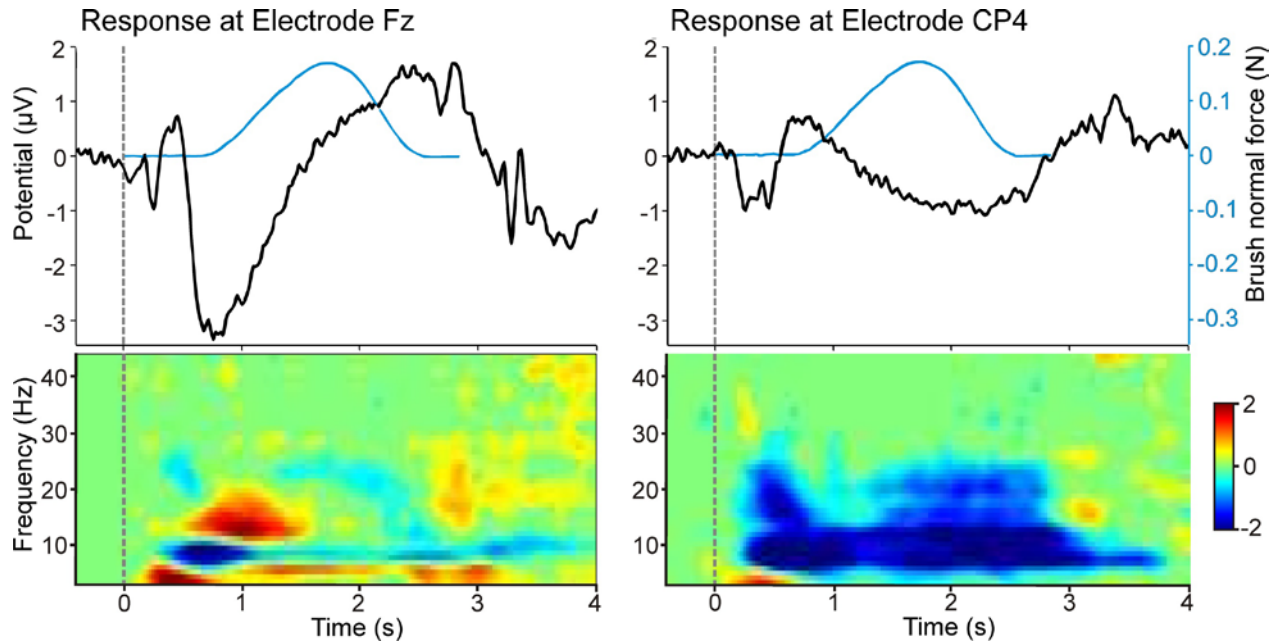


Figure 3: Comparison of responses from electrode Fz and electrode CP4. The top plots show the potential in μV of the responses over time (in black; the blue line represents the normal force of the brush) and the below ERSPs show the frequency responses over time in dB. There is a different neuronal and spectral response between the midline Fz electrode and electrode CP4, centered over the right (contralateral) sensorimotor cortex. Averaged data from the 11 participants in the main experiment.

The timing of the theta band event-related synchronization (ERS) seen in the frequency response from electrode Fz matched the time course of the ultra-late potential. It is likely that the transient beta synchronization reflects further processing of the A β fiber input, as it occurs later than the initial A β response but before the CT input arrives in the brain. The early potential peaks in electrode CP4 relates to the arrival of the fast A β input, however, as described above, these brush-evoked potentials have a slower time course compared to electrical somatosensory evoked potentials. From the start of these early peaks to the end of the brush stroke, long-lasting, event-related alpha (μ) desynchronization was seen, corresponding to the ongoing A β fiber input from the brush stimulating the hairs and skin. Beta desynchronization was also seen in the early part and at the end of the alpha band response, which was more closely related to the onset and offset of the brush stimulus. The early components occurring before 1.2 s in the potential and frequency response seen in electrode Fz also likely relate to the processing of the initial A β input.

Discussion

In the present paper, we focus on identifying the comparatively late somatosensory input from CT afferents activated by brush stroking on the arm in EEG. We provide the first demonstration of an ultra-late, positive potential that correlates with this innocuous C-tactile input. The CT ultra-late potential relates to those previously seen during laser activation of slowly conducting pain afferents [4, 5, 15], however in the present study, no painful stimuli were used to evoke the potential. This has advantages for the clinical exploration and diagnoses of afferent degeneration, such as in diabetes and other types of neuropathy. The data showed potentials from A β myelinated input and the unmyelinated CT input, which were clearly separated and did not interfere with each other, unlike A δ and C inputs in pain recordings [4, 5]. Therefore, neuropathies could be investigated without the need for painful stimuli or having tests based on temperature thresholds which rely on psychophysical feedback from the patient, especially for distinguishing between myelinated and unmyelinated tactile input. No special analyses were used to visualize the ultra-late potential, apart from having a high-pass filter of 0.1 Hz, so not to filter out the progression of the potential. Although the amplitude of the potential is very small (1-2 μ V), it was nevertheless possible to see it in every subject, with sufficient numbers of brush strokes (>150 included trials). In 3 subjects the potential was smaller than the other subjects, although nevertheless distinguishable in their averages. The time course of the ultra-late potential in the present study relates well to microneurography findings from single unit recordings of CTs; furthermore, the modulation of the response to faster and slower brush strokes showed that the ultra-late potential was specifically related to the stimulus. In exploratory experiments, we found that no ultra-late potential was found using a non-preferential CT stimulus (30 cm/s brushing [38]) or on the glabrous skin on the hand (where CTs have never been found) in a sub-population of subjects. The properties of CT afferents e.g. slow conduction velocity, inherent variability in the firing and their projection to the insula and frontal brain areas, but not SI, fit well with the ultra-late, slow potential seen in the ERP.

The opposing temporal properties of A β and C fiber tactile information are likely to be the basis for the mechanism of information processing i.e. the fast, A β fiber input activates SI, whereas the slower CT input does not [25, 26]. In the present study, differences were seen in the ERSPs relating to the brush stroke: the ultra-late potential was associated with an increase in theta ERS. These mechanisms may also relate to each other in the general processing and integration of somatosensory input. Neuronal activity in SI has been shown to oscillate synchronously in the alpha/mu range when no somatosensory input is present, and oscillate

desynchronously with somatosensory input [9, 23, 27, 28, 30]. The present data also finds that this idle, resting-state synchronicity is disrupted when SI is activated by a tactile input to the arm and it becomes desynchronized. The change in the synchronicity of SI oscillatory activity most likely underpins the mechanisms for processing the high temporal resolution myelinated input. Furthermore, it is also likely that due to differences in the temporal resolution between A and C tactile input, the lower temporal resolution CT input will be processed in a different way: such as the change to synchronous firing, as seen in the frontal theta ERS. Previous studies have found that frontal theta EEG power increases in a wide variety of situations, including somatosensory input [8], and increases in theta have been shown as a direct consequence of a decrease in the resting state network [31].

Conclusions

The present study shows an ultra-late, positive potential in the EEG, which corresponds to the longer-latency C-tactile fiber somatosensory afferent input. Evidence is presented that relates the time course of this ultra-late potential to the time course of the brush stimulus. The response from CT input was identified as an ERP and frequency response. The identification of this ultra-late somatosensory potential is also of clinical importance and may aid in the diagnosis of small-fiber afferent degeneration.

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