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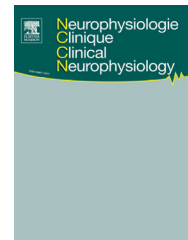
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ORIGINAL ARTICLE/ARTICLE ORIGINAL

Pneumatic evoked potential. Sensory or auditive potential?

Le potentiel évoqué pneumatique. Potentiel sensoriel ou auditif?

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KEYWORDS

Pneumatic evoked potentials;
Methodology;
Somatosensory system;
Multimodal integration

Summary

Study aim. – In this study, evoked potentials (EPs) to a pneumatic, innocuous, and calibrated stimulation of the skin were recorded in 22 volunteers.

Methods. – Air-puff stimuli were delivered through a home-made device (INSA de Lyon, Laboratoire Ampère, CHU de Saint-Étienne, France) synchronized with an EEG recording (Micromed®).

Results. – A reproducible EP was recorded in 18 out of 22 subjects (82% of cases) with a mean latency of about 120–130 ms, and maximal amplitude at Cz. This EP actually consisted of two components, an auditory and a somatosensory one. Indeed, it was significantly decreased in amplitude, but did not disappear, when the noise generated by the air-puff was masked. We also verified that a stimulation close to the skin but not perceived by the subject was not associated with any EP. Conduction velocity between hand and shoulder was calculated around 25 m/s.

Conclusions. – This preliminary study demonstrates that pneumatic EPs can be recorded in normal volunteers.

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Résumé

Buts de l'étude. – Dans cette étude, nous avons enregistré, chez 22 volontaires sains, le potentiel évoqué (PE) à une stimulation pneumatique calibrée délivrée sur la peau.

Méthodes. – Le stimulateur est un prototype qui permet de générer une sensation indolore de courant d'air sur la peau, synchronisé avec un appareil d'acquisition de PE (Micromed®).

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Somesthésie ;
Méthodologie ;
Intégration
multimodale

Résultats. – Cette stimulation pneumatique induit un PE somesthésique de latence moyenne de 120 à 130 ms, maximal sur l'électrode Cz et se distribuant à l'ensemble du scalp. Ce PE est obtenu de manière reproductible chez 18 sujets, soit dans 82 % des cas. Vu qu'il est significativement diminué d'amplitude mais ne disparaît pas lorsque l'on masque le bruit émis par le stimulateur, on en déduit qu'il est constitué de deux composantes, l'une auditive, l'autre somesthésique. On a pu valider qu'il était bien lié à la stimulation somesthésique car en stimulant à côté de la main, le potentiel disparaît. La vitesse de conduction mesurée entre deux sites, l'un proximal sur l'épaule, l'autre distal sur la main, est de l'ordre de 25 m/s.

Conclusions. – Il est possible d'enregistrer des potentiels évoqués pneumatiques par stimulation cutanée chez le sujet normal.

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Introduction

Somatosensory evoked potentials (SEPs) have been traditionally and historically recorded through peripheral stimulation of large myelinated fibres by an electric current applied to nerve trunks, for example, the median or the ulnar nerve in the upper limbs [3–5,7]. Thermal or laser stimulators capable of generating painful sensations were developed to activate peripheral pain receptors and produce nociceptive EPs [2,13,14]. The capacity for pneumatic stimulations to produce an EP has been tested before, but only on rare occasions [9,10,12,15] and without any subsequent use in clinical practice. In this study, EPs were recorded with a prototype consisting of a compact pneumatic stimulator, which delivers a calibrated compressed air jet and produces a draught sensation on the skin. Considering that skin stimulation was systematically associated with an air propulsion noise, we wanted to ensure that the obtained responses did not only correspond to an auditory evoked response. By measuring the conduction velocity between two stimulation sites in 22 volunteers, we attempted to determine through which type of nerve fibres the recorded signals were transmitted.

Material and methods

Patients

Twenty-two healthy volunteers (12 women, 10 men, mean age: 22.8 ± 8.7 years, range 18 to 44) participated in this study. The only exclusion criteria were a history of psychiatric or neurological disease.

Stimulator

For this study, we developed a pneumatic stimulator, which includes a nozzle, an electropneumatic distributor placed in an adapted casing, and a pneumatic energy source with a pressure of 3.5 bars. The air outlet of the nozzle is 0.5 mm in diameter and delivers sterile pulsed air (less than 10 ms in duration), which is dispersed to produce a draught. Pulsed-air delivery produces a small noise of 45–55 dB. Stimulation frequency was 0.2 Hz with fixed inter-stimulus interval. The stimulator was placed perpendicularly to the skin at a minimum distance of 1 cm and a maximum one of 2 cm. All stimulations were applied on the right side, distally on the back of the hand (at equal distance between the base of the

third finger and the wrist) and proximally on the shoulder (rise of the deltoid muscle).

Data acquisition

EPs were recorded with a cap including 19 active electrodes distributed over the scalp according to the International 10-20 EEG System. The reference electrode was placed on the nose and the ground one on Fpz. Electrode impedance (lower than $3 \text{ k}\Omega$) was checked before starting acquisitions. The electrooculogram (EOG) was recorded with two electrodes placed at the external canthus of the left eye. Signals were acquired with a Micromed System Plus analysis system (band pass: 0.3–100 Hz; sampling frequency: 512 Hz; analysis time: 1 s; threshold for artifact rejection: $75 \mu\text{V}$, in addition to manual rejection). Stimuli were triggered by the acquisition system via a TTL signal sent to the pneumatic stimulator. EP acquisition started at the moment of pulsed-air delivery.

Volunteers were comfortably lying in a quiet room with soft lighting. They were asked to relax. In order to rule out the possibility that responses would actually consist of a spurious contamination by an auditory EP generated by the intermittent noise of the stimulator, in half of these manipulations, we acoustically isolated the subject by making him/her listen to a white noise through an auditory helmet that totally masked the air jet noise.

Experimental paradigm

The study consisted of six series of 30 pneumatic stimulations (Fig. 1). Each series was recorded twice in order to ensure reproducibility. The six series corresponded to the following six experimental conditions:

- Condition A = proximal + auditory: pneumatic stimulations applied on the shoulder, no auditory masking;
- Condition B = proximal alone: pneumatic stimulations applied on the shoulder, auditory masking;
- Condition C = distal + auditory: pneumatic stimulations applied on the hand, no auditory masking;
- Condition D = distal alone: pneumatic stimulations applied on the hand, auditory masking;
- Condition E = auditory alone: air jet directed beside the hand, no auditory masking;

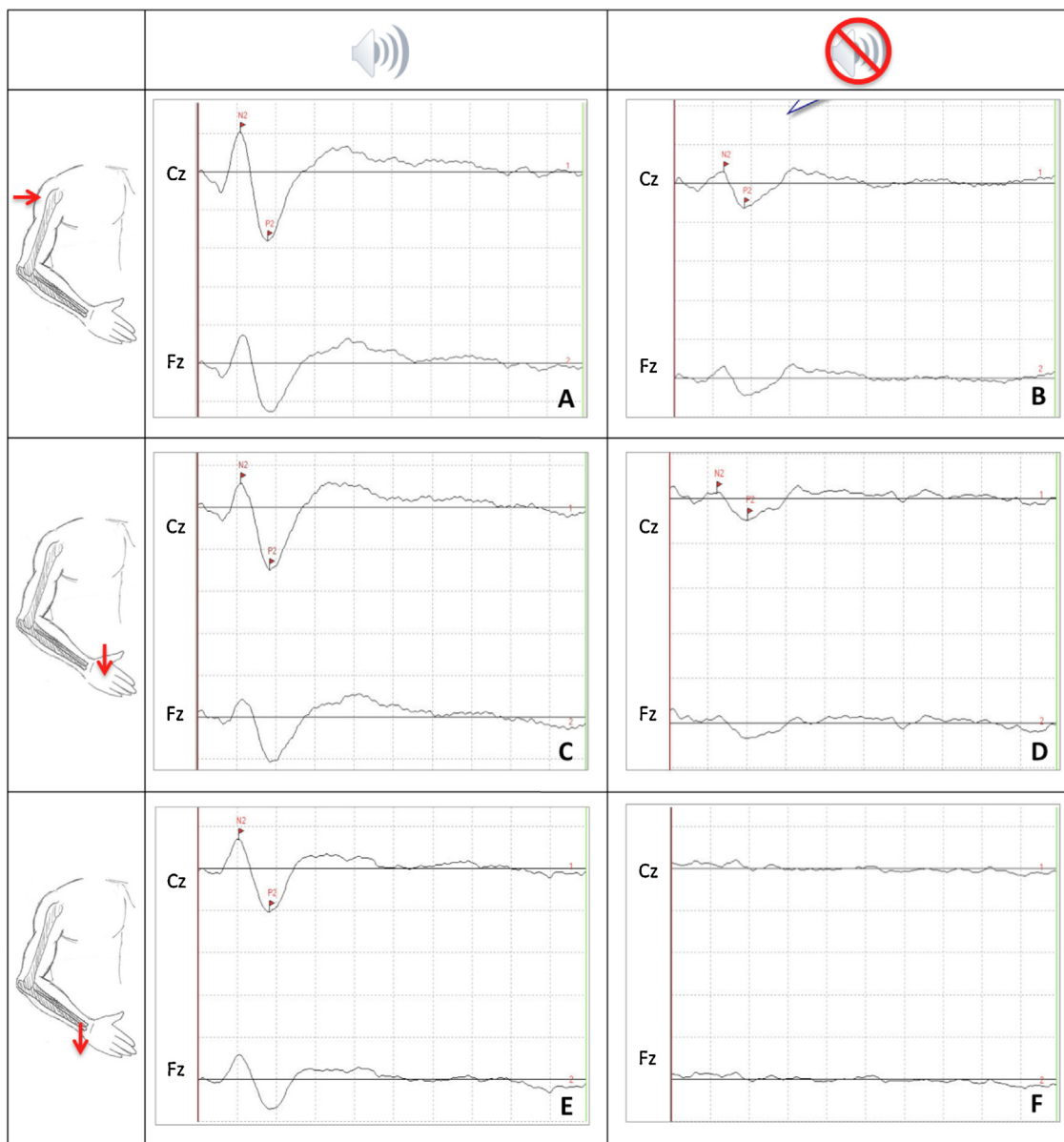


Figure 1 Responses to pneumatic stimulation: overall waveform aspect. Each waveform corresponds to the grand average of the evoked potentials (EPs) obtained at Cz and Fz in the 18 volunteers for each condition (left columns: no auditory masking; right column: auditory masking). The pneumatic stimulation is directed on shoulder (upper line), hand (second line), or beside the hand (lower line). A: proximal + auditory: pneumatic stimulations applied on the shoulder, no auditory masking; B: proximal alone: pneumatic stimulations applied on the shoulder, auditory masking; C: distal + auditory: pneumatic stimulations applied on the hand, no auditory masking; D: distal alone: pneumatic stimulations applied on the hand, auditory masking; E: auditory alone: air jet directed beside the hand, no auditory masking; F: no stimulation (control condition): air jet directed beside the hand, auditory masking.

- Condition F = no stimulation (control condition): air jet directed beside the hand, auditory masking.

Data analysis

Since each series was recorded twice, all non-reproducible series were eliminated from the analysis. The series corresponding to the F-condition (no stimuli) were not taken into account in the statistical analysis.

N_2 and P_2 latencies (in ms) and N_2P_2 peak-to-peak amplitudes (in μV) were measured on the electrode providing the response with the highest amplitude. Conduction velocities were calculated according to the following formula: [hand-shoulder distance (in meter)]/[N_2 latency in Condition D or C (hand stimulation) – N_2 latency in Condition B or A (shoulder stimulation) (in second)].

SPSS Version 16 software was used for statistical analyses. A Kolmogorov-Smirnov test was used to check variable normalcy, authorizing use of parametric statistical tests.

Table 1 Amplitude and latencies of evoked potentials (EPs) for each condition.

| Conditions | Amplitude of N2P2 | Latency of N2 | Latency of P2 |
|------------|-------------------|---------------|---------------|
| A | | | |
| Mean | 16 | 109 | 173 |
| <i>n</i> | 18 | 18 | 18 |
| SD | 8.8 | 12 | 15 |
| Min | 5.5 | 90 | 158 |
| Max | 32.7 | 131 | 197 |
| B | | | |
| Mean | 5.8 | 120 | 176 |
| <i>n</i> | 18 | 16 | 16 |
| SD | 4.7 | 17 | 22 |
| Min | 0 | 90 | 137 |
| Max | 16.5 | 146 | 219 |
| C | | | |
| Mean | 12.4 | 117 | 181 |
| <i>n</i> | 18 | 18 | 18 |
| SD | 7.4 | 17 | 16 |
| Min | 4.4 | 92 | 146 |
| Max | 26.7 | 146 | 217 |
| D | | | |
| Mean | 4.3 | 130 | 195 |
| <i>n</i> | 18 | 12 | 12 |
| SD | 4.6 | 28 | 36 |
| Min | 0 | 70 | 137 |
| Max | 13.9 | 184 | 273 |
| E | | | |
| Mean | 9.5 | 105 | 179 |
| <i>n</i> | 18 | 17 | 17 |
| SD | 5.4 | 13 | 14 |
| Min | 0 | 90 | 154 |
| Max | 20.2 | 146 | 199 |

A: auditory + pneumatic stimulation on shoulder; B: pneumatic stimulation alone on shoulder; C: auditory + pneumatic stimulation on hand; D: pneumatic stimulation alone on hand; E: auditory stimulation alone.

The significance threshold was set at $P \leq 0.05$. Conduction velocities for the “pneumatic and auditory” stimulations (conditions A and C) and for the “pneumatic alone” stimulations (conditions B and D) were compared using the Mann-Whitney test for independent samples. N₂ and P₂ latencies and N₂P₂ amplitudes at Cz under the five conditions (A, B, C, D and E) were compared using a one-factor Anova. In case of $P < 0.05$, post-hoc analyses (Bonferroni’s test) were carried out. A Pearson’s test was used to examine correlations between individual heights and N₂ or P₂ latencies, and individual ages and N₂P₂ amplitudes.

Results

Individual analyses

In four subjects, responses were too noisy and/or their reproducibility was too low for one or more conditions, so that their data were not included. At least one reproducible and interpretable response was obtained in 18 out of 22 subjects (82% of the population). Individual responses were obtained in 18 subjects when the noise of the pneumatic

stimulation was not masked (conditions A and C). When the noise of stimulation was masked (conditions B and D), a response to pneumatic stimulation of the shoulder or the hand was found in 16 and 12 subjects, respectively. Seventeen subjects had a response to the noise of stimuli (condition E: auditory alone) (Table 1).

Overall response description

Whenever obtained, responses were maximal at Cz. These consisted of a first negative component, which we will refer to as N₂, and a second positive component, which we will refer to as P₂ (Fig. 1). Grand-mean latencies and amplitudes of both peaks in the different conditions are shown in Table 1.

Group analysis: effect of conditions

The 1-factor Anova test demonstrated a condition effect on N₂P₂ amplitude ($F = 9.95$; $P < 0.0001$), which was higher in conditions without (conditions A and C) versus with (conditions B and D) auditory masking. Amplitude differences of

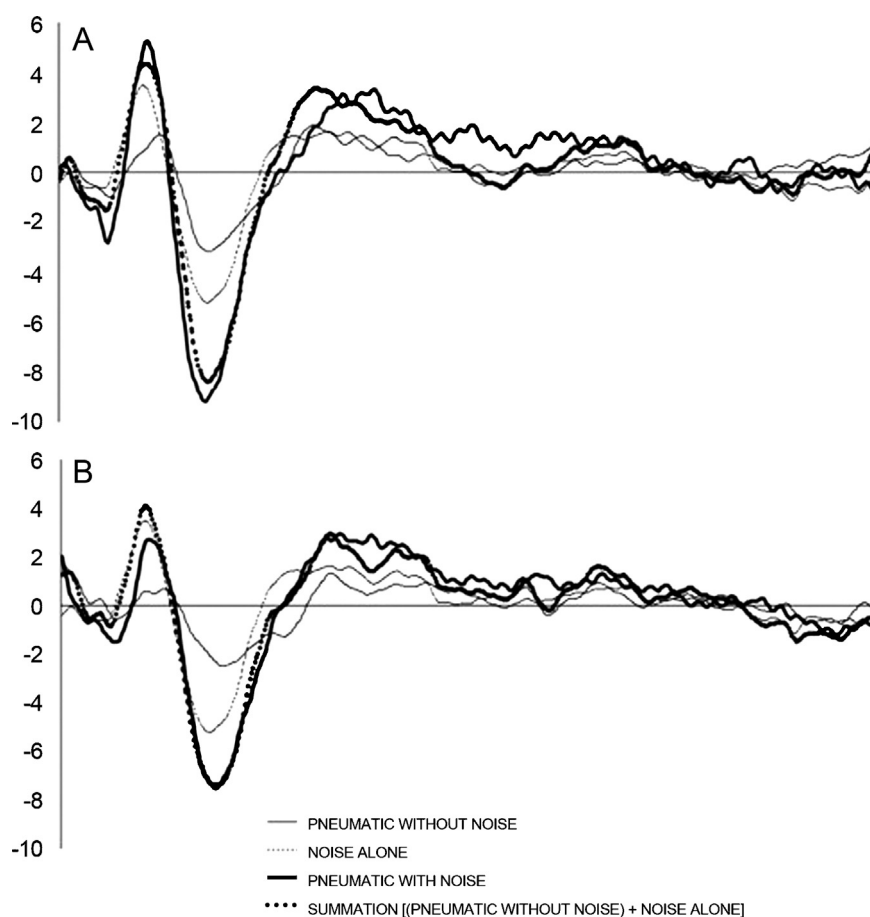


Figure 2 Dissociation of auditory and somatosensory evoked potentials (EPs). The waveforms obtained in response to combined auditory and pneumatic stimulation (full continuous) are compared with the algebraic summation (full dotted) of waveforms obtained in the “auditory alone” (thin dotted) and “pneumatic alone” (thin continuous) conditions (A: shoulder stimulation; B: hand stimulation). Both waveforms do not differ from each other, which argues for mere linear combinations of responses to auditory and somatosensory stimulation without any non-linear interaction. Note that responses to auditory stimulation always occurred earlier than responses to pneumatic stimulation, irrespective of the stimulation site (analysis time: 500 ms; Y-axis in μV).

10.2 μV ($P < 0.001$) and 8.1 μV ($P = 0.003$) were found after shoulder and hand stimulation, respectively. Noteworthy reproducible EPs were obtained in both auditory alone (E) and pneumatic alone (B and D) conditions. These EPs all have the same scalp distribution and nothing in their topography enables distinguishing them from each other (at least with the spatial sampling we used). As expected, no reproducible responses were obtained in the F-condition (no stimulation at all).

In Fig. 2, we compared responses obtained in the “pneumatic+auditory” A (proximal) and C (distal) conditions with the algebraic sums of responses obtained in the E (auditory alone) and, respectively, the B and D conditions (pneumatic alone). These recorded and calculated responses did not significantly differ from each other ($P = 0.5$ and $P = 0.32$ after proximal and distal stimulation, respectively).

Conduction velocities

In the “pneumatic alone” conditions (B and D), hand-to-shoulder conduction velocities were measurable in eight

subjects, with a mean value of 25 ± 14 m/s. When performing the same calculation in the “auditory + pneumatic” conditions (A and C), a significantly higher value (59 ± 32 m/s) was obtained (Mann-Whitney test for independent samples: $W = 54$, $P = 0.013$).

Discussion

In this study, we aimed to verify whether pneumatic stimulation of the skin could generate an EP. The answer is, indeed, affirmative for the vast majority of tested subjects. However, it should be noticed that four healthy subjects either had no response or responses that might be absent on some body segments. The following hypotheses can *a priori* be put forward to explain this result:

- the technical recording difficulties that are inherent to the development of any new stimulation technique;
- suboptimal relaxation in some volunteers;
- artifacts (a common problem in any EP recording);
- and most likely, some response habituation to repeated stimuli.

According to the experience we gained throughout this pilot study, this failure to get reproducible EPs in some individuals is more likely due to signal recording or analysis issues than to the actual absence of pneumatic EPs in some individuals.

Auditory or somatosensory EPs?

Previous attempts to get pneumatic EPs [9,10,15] identified EPs that were similar to the one we recorded, in both terms of latency and topography. However, these studies did not consider the possibility of a contamination by an auditory EP in response to the noise generated by the pneumatic stimulation. Noteworthy, these EPs have a latency that is relatively close to that of nociceptive EPs to laser stimulation [1,13,14] or late components of somatosensory EPs [4,5], but also compatible with that of the N_{100} component of cortical auditory EPs [11]. Therefore, even if it is most likely that these EPs do not correspond to primary brain responses such as the SEP N_{20} or the AEP N_aP_a peak, but rather to a secondary process, this questions the actual somatosensory nature of the obtained EPs.

By masking the stimulus-related noise, we were able to demonstrate that pneumatic stimulation of the hand or shoulder induced an EP that was specific of pneumatic stimulation. Therefore, this study actually validates this type of pneumatic stimulator as a possible new tool to enrich the inventory of tested somatosensory function, provided that auditory afferences should be masked by a white noise.

However, without auditory masking, the EP was obviously a mixture of auditory and somatosensory components. This raises the issue whether these mixed responses merely correspond to a linear superimposition of auditory and somatosensory components or whether these also reflect some non-linear interaction between both types of stimuli. This issue is worth being considered as the combination of a response from an auditory source to the response from a somatosensory source could cause some attentional phenomena, which are known to increase EP amplitude [6–8]. The absence of any significant difference between EPs obtained in response to combined somatosensory and auditory stimuli, and the algebraic sum of EPs obtained in response to isolated auditory and somatosensory stimulation argue in favour of a mere linear superimposition of responses, without any detectable non-linear interaction.

Conduction velocities

Comparison of distal to proximal latencies led to different estimations of conduction velocities according to whether they were measured in the absence (59 m/s) or in the presence (25 m/s) of auditory masking. A plausible explanation would be that the response obtained in the absence of auditory masking corresponds to the linear combination of auditory (auditory N_{100}) and somatosensory component, so that the difference in measured conduction velocities would actually be some matter of mathematical artifact depending on the shorter latency of the auditory response (Fig. 2). Briefly, the peak of the “pneumatic alone” (D) condition for the hand has a 130 ms latency while the peak of the auditory N_{100} (E) condition has a 105 ms latency (Table 1). The

linear combination of these two responses predicts an intermediate latency for the peak combining a pneumatic and an auditory component, what is verified in the C condition (117 ms). A similar argument can be used for the stimulation of shoulder: The latency of the auditory response for a sound applied to the shoulder should be shortened by 2 ms (103 ms) as compared to the hand (105 ms), corresponding to the speed for sound propagation in a distance between hand and shoulder (56 cm). The linear combination of the response for the “pneumatic alone” (B) condition (120 ms) and the auditory response for the shoulder predicts a 111 ms that is very close to the 109 ms latency observed in the A condition. The difference in latencies according to whether the noise is masked or not masked ($130 - 105 = 25$ ms or $117 - 103 = 14$ ms, respectively) implies a two-fold difference in the calculation of the conduction velocity, this latter being falsely increased because of the auditory component. Thus, the conduction velocity that seems appropriate is the one obtained in the “pneumatic alone” conditions and it is estimated around 25 m/s.

Perspectives

Such conduction velocity indicates that the corresponding peripheral fibres actually conduct more slowly than those concerned by nerve electrical stimulation in classical SEP recordings. This result is unexpected since we hypothesized that pneumatic stimulation of touch-sensitive receptors would be conveyed by large myelinated A-beta fibres. Actually, such conduction velocity would rather correspond to fibres that would be intermediate between large myelinated fibres and these sparsely myelinated A-delta fibres that are solicited by laser stimulation. It remains however to be established by another experimental setting whether the EPs presented here are preceded (or not) by an early EP. This prototype shows that a somatosensory pathway that is distinct from that of SEPs can be tested using superficial cutaneous stimulation by pulsed air. Pneumatic EPs could be used in conjunction with SEPs and Laser Evoked Potentials (LEPs) to classify the patients with neuropathic pain according to the types of fibre and conduction abnormalities. Their use in allodynic patients could enable the description of abnormal responses in patients suffering from neuropathic pain in response to a painless tactile stimulation, cooled if necessary, to sensitise the stimulation. The use of a MRI-compatible stimulator will enable its development for scientific research in the field of neuropathic pain.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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