

Mismatch responses evoked by nociceptive stimuli

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Abstract

We studied whether nociceptive mismatch negativity (nMMN) could be obtained as result of nociceptive fibers stimulation. The purported nMMN revealed a topography similar to the somatosensory MMN (sMMN), which was observed at the bilateral temporal regions of the scalp. Importantly, only early negativities (100–250 ms) located at these regions revealed a selective modulation associated to the processing of deviancy regardless of the attentional focus. The amplitude modulation of the sMMN had an earlier onset than the nMMN (110 ms vs. 182 ms) as well as a larger difference of latency between the contralateral and the ipsilateral onset of the activity (52 ms vs. 4 ms). Altogether, these observations provide evidence that (a) a nMMN can be elicited by nociceptive stimuli, and (b) the nMMN is topographically similar to the sMMN while differing in latency and possibly in functional organization of their generators.

Descriptors: Mismatch negativity, Somatosensory system, Nociceptive system, Attention, Electroencephalography

Typing the keyword “mismatch negativity” (MMN) on PubMed returns more than 1,500 records, thus confirming it as one of the most investigated topics in neurophysiology since its earliest description (Naatanen, Gaillard, & Mantysalo, 1978). Its success in drawing researchers’ interest is mostly determined by the progressive amount of evidence pinpointing it as an objective index of perceptual processes, due to its functional independence from voluntary attention (Naatanen et al., 2012). Traditionally, MMN is evoked by a deviant or rare (i.e., oddball) event embedded in a stream of repeated or familiar events (i.e., standards), which can be noninvasively recorded using electroencephalography (EEG) and magnetoencephalography (MEG).

Consensus is established on the notion that MMN is an index of automatic change detection regulated by a preattentive sensory memory mechanism (Tiitinen, May, Reinikainen, & Naatanen, 1994; Winkler, Reinikainen, & Naatanen, 1993). Such agreement originates from a bulk of research on MMN elicited by auditory stimuli (and stimuli features). When evoked by auditory stimuli, MMN peaks at about 100–250 ms from change onset and exhibits a low amplitude of no more than 5 μ V, with a temporal-frontal topography (e.g., Sams et al., 1985) thought to be at least partially

generated from the auditory region of the supratemporal cortex (e.g., Giard, Perrin, Pernier, & Bouchet, 1990; Shalgi & Deouell, 2007). Several studies reported the existence of a visual MMN counterpart at about 150–250 ms, and triggered by changes of stimulus movement, form, and orientation, among other physical features (e.g., Czigler, Balazs, & Pato, 2004; Kimura, Ohira, & Schroger, 2010). Conversely, it is difficult to track down similar evidence concerning mismatch responses elicited by somatosensory stimuli. Indeed, only a few studies of mismatch-related cortical responses following electrical or vibratory input have been published. In a pioneer study, Kekoni et al. (1997) reported evidence of a somatosensory MMN (sMMN) occurring between 150 and 250 ms following deviant vibration bursts, which was further confirmed by other researchers using MEG (Akatsuka et al., 2007).

Crucially, as a matter of fact, no study to date has reported the existence of a mismatch phenomenon exerted through the selective stimulation of A δ nociceptive fibers. Given the current quest for an objective neuronal marker of pain sensitivity (Schulz, Zherdin, Tiemann, Plant, & Ploner, 2012; Tracey, 2011), it is surprising that an attention-independent index of sensory change has not been investigated yet in the field of pain. In fact, among the cognitive variables affecting pain experience, the brain mechanisms underlying attentional control have probably been the most extensively studied (see Van Damme, Legrain, Vogt, & Crombez, 2010, for a review). Yet, no evidence suggests the existence of a nociceptive attention-independent brain response, even at the earliest latency of neural activation (i.e., the N1 wave of laser-evoked potentials; see Lorenz & Garcia-Larrea, 2003).

Since a preattentive electrophysiological index of nociceptive-related brain activity would benefit in both basic and clinical pain studies, here we aimed (a) to identify a nociceptive MMN (nMMN) as compared to sMMN in the context of a roving paradigm (e.g.,

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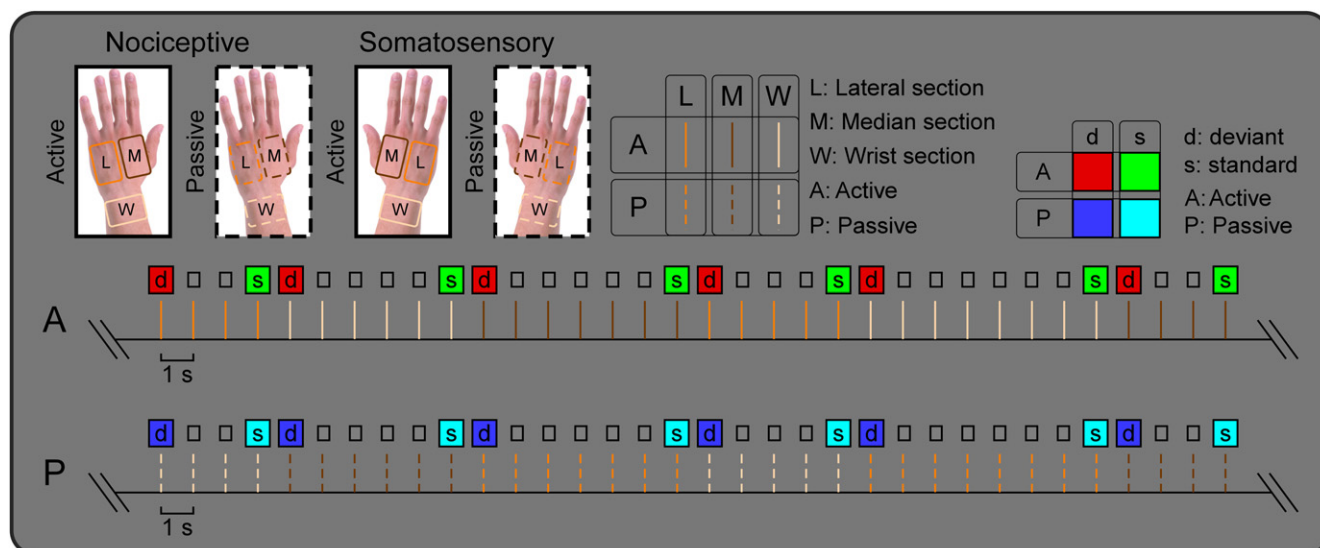


Figure 1. Experimental design. Event-related potentials were recorded in four sessions (two modalities: non-nociceptive somatosensory and nociceptive stimuli; two conditions: active and passive) (top left), and two repeated blocks were included in each session. Block order was counterbalanced across participants. In each block, trains of non-nociceptive somatosensory and nociceptive stimuli were delivered to lateral (L), median (M), or wrist (W) section of the participants' right and left hands, respectively (top left and top central). Each block had about 50 trains of stimuli with an intertrain interval of 1,000 ms. Each train consisted of 4–8 repeated identical stimuli delivered to the same section at a constant interstimulus interval of 1,000 ms (bottom). In each modality, participants were required either to focus their attention on the stimuli in two blocks (A: active condition), or to focus their attention on watching a silent video in the remaining two blocks (P: passive condition). The first stimulus in each train was a deviant (d) that became a standard (s: the last stimulus in each train) through repetition. This design provided four conditions (Ad, As, Pd, and Ps; top right). In this paradigm, deviants and standards had exactly the same number of trials and physical properties. Note that in each train the stimuli (gray squares) between deviant and standard were omitted from the data analysis (bottom).

Boly et al., 2011; Garrido et al., 2008; Haenschel, Vernon, Dwivedi, Gruzelić, & Baldeweg, 2005), and (b) to discriminate the cortical effects associated to a somatosensory/nociceptive change against the effects of attending such a change in the environment.

Method

Participants

EEG data were collected from 15 healthy, right-handed volunteers (seven males and eight females) aged 21 ± 1.6 (mean $\pm$ SD, range = 19–24 years). All participants gave their written informed consent and were paid for their participation. The local ethics committee approved the procedures, which were in accordance with the standards of the Declaration of Helsinki.

Stimulation

Non-nociceptive somatosensory and nociceptive stimuli were delivered on the participants' right and left hands, respectively. Participants were first familiarized with both non-nociceptive and nociceptive stimuli, then a sensory threshold assessment took place whereby the energy of non-nociceptive and nociceptive stimuli was adjusted individually using the method of limits. Non-nociceptive somatosensory stimuli (i.e., transcutaneous electrical stimuli, TES) consisted of three rapidly succeeding constant-current square-wave pulses (0.5-ms duration) delivered through a pair of surface electrodes (2-cm distance between electrodes). The interpulse interval was 12 ms. The stimulus intensity was twice the individual perceptual threshold, an intensity classically used to activate the A β fibers in humans (Garcia-Larrea, Lukasiewicz, & Mauguire, 1995; Hu

et al., 2011). These stimuli elicited a vibratory sensation and were never reported as painful. Nociceptive stimuli (i.e., intraepidermal electrical stimuli, IES) consisted of three rapidly succeeding constant-current, square-wave pulses (0.5-ms duration) delivered through three stainless steel concentric bipolar needle electrodes (located according to an equilateral triangle shape). Each of the electrodes consisted of a needle cathode (length: 0.1 mm, $\varnothing$: 0.2 mm) surrounded by a cylindrical anode ($\varnothing$: 1.4 mm) (Inui, Tran, Hoshiyama, & Kakigi, 2002; Inui, Tsuji, & Kakigi, 2006). The interpulse interval was 12 ms. The stimulus intensity was twice the individual perceptual threshold, an intensity that proved to preferentially activate the A δ nociceptive fibers without simultaneously activating the A β fibers (Mouraux, Iannetti, & Plaghki, 2010). These stimuli elicited a painful pinprick sensation in all participants.

Experimental Design and Procedure

A schematic illustration of the experimental design is shown in Figure 1. Participants were seated on a comfortable chair in a silent, temperature-controlled room. Somatosensory and nociceptive evoked potentials (SEPs and NEPs) were evoked by trains of non-nociceptive TES and nociceptive IES delivered to the lateral (L), median (M), or wrist (W) section of the participants' left and right hands, respectively (Figure 1, top left; see Legrain, Perchet, & Garcia-Larrea, 2009, for a reference to such spatial partitioning of the hand's stimulation area). All participants had no difficulty in distinguishing the stimuli at the three sites for both non-nociceptive TES and nociceptive IES.

SEPs and NEPs were recorded either while the participants were attending to (active condition), or were distracted from

(passive condition), the sensory stimulation (Figure 1, top left). SEPs and NEPs were collected during eight experimental blocks. Two blocks were repeated for each modality and each experimental condition, thus providing four blocks per modality and four blocks per condition in total. The order of all blocks was counterbalanced across participants. In active blocks, participants were instructed to focus on the stimuli and required to report the total number of the stimuli at the end of each block. If the participants could not report the total number of stimuli or reported a wrong value, the corresponding active block was discarded and restarted. This rule was followed until an accurate value was provided by the participants. In addition, at the end of each active block, participants were required to rate verbally the average intensity of the sensation associated to non-nociceptive somatosensory and nociceptive stimuli, using a numerical rating scale ranging from 0 to 10, where 0 was *no sensation/no pain* and 10 was *unbearable sensation/unbearable pain*. In passive blocks, participants were instructed to watch a silent video with subtitles, and required to answer general and specific questions in a structured interview taking place at the end of each passive block.

Each block contained about 50 trains of stimuli with an inter-train interval (ITI) of 1,000 ms. The total number of trains for each condition (active or passive) in each modality (somatosensory or nociceptive) was 100. In each train, 4 to 8 repeated identical stimuli (the number of stimuli in each train was pseudorandomly distributed across trains) were delivered to the same hand's section with an interstimulus interval (ISI) of 1,000 ms. Each hand section had the same number of trains across subjects ($n = 33.3 \pm 0.5$ for each condition and each modality). Note that in each block the number of trains was kept constant across the different types of trains ($n = 10$; train length ranging from 4 to 8 stimuli).

The sensory events were administered according to a standard roving paradigm (see Garrido et al., 2008, for a detailed discussion). The first stimulus in each train was a deviant (d) that became a standard (s: the last stimulus in each train) through repetition. In other words, each train of stimulation started with a deviant stimulus delivered on one of the three different hand's sections (Figure 1, bottom). This paradigm ensured that deviants and standards had exactly the same number of trials and physical properties.

EEG Recording

The EEG data were recorded using a Brain Products system (band-pass: 0.01–100 Hz, sampling rate: 500 Hz), connected to a standard EEG cap with 60 scalp Ag-AgCl electrodes placed according to the International 10-20 system. The left mastoid was used as reference channel, and all channel impedances were kept below 5 k Ω . To monitor ocular movements and eye blinks, electrooculographic (EOG) signals were simultaneously recorded from four surface electrodes placed on the upper and lower eyelid, and next by the outer canthus of the left and right eye.

Data Analysis

Psychophysics. In the active condition, the average ratings of the sensation elicited by non-nociceptive somatosensory and nociceptive stimuli were compared across different stimulus sites using one-way repeated measures analysis of variance (ANOVA) with 3 within-subject levels (L, M, and W sections). Statistical significance was set at $p < .01$. Mauchly's test was applied to assess the possible violations of sphericity. If the assumption of sphericity was violated ($p < .01$), the degrees of freedom were adjusted

($\epsilon < 0.75$: Greenhouse-Geisser correction, $\epsilon > 0.75$: Huynh and Feldt correction). When the main effect of the ANOVA was significant, Tukey pairwise post hoc comparisons were performed.

EEG data preprocessing. EEG data were processed using EEGLAB (Delorme & Makeig, 2004), an open source toolbox running in the MATLAB environment. Continuous EEG data were low-pass filtered at 30 Hz. EEG epochs were extracted using a time window of 700 ms (200 ms prestimulus and 500 ms poststimulus) and baseline corrected using the prestimulus interval. Trials contaminated by eyeblinks and movements were corrected using an Independent Component Analysis (ICA) algorithm (Delorme & Makeig, 2004; Jung et al., 2001). In all datasets, these independent components had a large EOG channel contribution and a frontal scalp distribution. After ICA, epochs were baseline corrected once more using the prestimulus interval, and rereferenced to a common average reference.

In each participant, epochs belonging to the same experimental condition were averaged together (regardless of the stimulation site) and were time-locked to the onset of the stimulus. This procedure yielded eight average waveforms in each participant (four waveforms for both SEPs and NEPs: active-deviant [Ad], active-standard [As], passive-deviant [Pd], and passive-standard [Ps]). Each participant's average waveforms were subsequently averaged to obtain group-level average waveforms. Group-level scalp topographies were computed by spline interpolation. Scalp topographies of SEPs in the four experimental conditions were plotted, in steps of 20 ms, from 80 ms to 300 ms. Similarly, scalp topographies of NEPs in the four experimental conditions were plotted, in steps of 20 ms, from 140 ms to 360 ms.

Statistical approach to somatosensory and nociceptive brain evoked potentials

Definition of spatial regions of interest (sROIs). A point-by-point, two-way repeated measures ANOVA was used to assess the effects of mismatch (two levels: deviant vs. standard) and attention (two levels: active vs. passive) on SEPs and NEPs, respectively, to define their significant sROIs.

This yielded three time-course waveforms of F values for each modality and channel representing (1) the main effect of mismatch, (2) the main effect of attention, and (3) the interaction between the two factors. Significant sROIs were defined based on the criteria that (a) they had to be composed of at least two nearby significant channels, and (b) they had to be composed of more than 10 consecutive significant time points (20 ms) for the factor mismatch and attention, respectively ($F > 8.9$, $p < .01$).

Definition of temporal regions of interest (tROIs) within each sROI. For each sROI that was significantly modulated by mismatch, we computed the average stimulus-evoked brain responses across all channels within the sROI for each participant and experimental condition (Ad, As, Pd, and Ps). The resulting average brain responses were submitted to a point-by-point, two-way repeated measures ANOVA, combined with nonparametric permutation testing (Maris & Oostenveld, 2007), to assess the time course of the effects of mismatch and attention on SEPs and NEPs, respectively. This was performed according to the following five steps. First, each time point of the stimulus-evoked brain responses averaged across channels in each spatial region was compared using a two-way repeated measures ANOVA, with mismatch (two levels: deviant vs. standard) and attention (two levels: active vs. passive) as factors. This yielded three time course waveforms of F values,

representing (1) the main effect of mismatch, (2) the main effect of attention, and (3) the interaction between the two factors. Time points with a p value $< .01$ ($F > 8.9$) were selected for subsequent analyses. Second, to account for the multiple comparison problem in the point-by-point statistical analysis (Maris & Oostenveld, 2007), significant time points ($p < .01$) were categorized in clusters based on their adjacency in the time course (cluster-level statistical analysis). Only clusters composed of more than 10 adjacent significant time points were considered (20 ms), to account for the problem of multiple comparisons. The sum of the F values of all time points composing a cluster defined its cluster-level statistics (ΣF). Third, for every participant, we randomly permuted 5,000 times the time course waveforms of the four conditions (Ad, As, Pd, and Ps). In each permutation, the same two-way repeated measures ANOVA was performed at every time point of the clusters identified in step two, thus yielding a cluster-level statistics $\Sigma'F(m)$ at the m th permutation. Permutation distributions $D(\Sigma F)$ of the cluster-level F statistics were obtained from $\Sigma'F(m)$. Fourth, for each cluster identified in the second step, its two-tailed p value pF was obtained by locating the observed ΣF under the permutation distribution $D(\Sigma F)$ estimated from permuted $\Sigma'F(m)$. Fifth, clusters were used to define tROIs for the subsequent quantitative analysis based on the criterion that the cluster had a p value smaller than a defined threshold ($pF < .01$) (Maris & Oostenveld, 2007).

For each identified sROI that was significantly modulated by attention, identical statistical analysis (point-by-point, two-way repeated measures ANOVA and nonparametric permutation testing) was performed to define the significant tROIs for SEPs and NEPs, respectively.

Statistical analysis within each tROI. In each mismatch and attention modulated tROI, the mean value of all time points within the tROI was computed for each participant and each experimental condition (Ad, As, Pd, and Ps). The obtained mean values were then compared using a two-way repeated measures ANOVA, with mismatch (two levels: deviant vs. standard) and attention (two levels: active vs. passive) as factors. Mauchly's test was applied to assess the possible violations of sphericity. If the assumption of sphericity was violated ($p < .01$), the degrees of freedom were adjusted ($\epsilon < 0.75$: Greenhouse-Geisser correction, $\epsilon > 0.75$: Huynh and Feldt correction).

In mismatch modulated sROIs, when the interaction was significant, post hoc Tukey's HSD test was performed to compare the responses obtained in the four experimental conditions (Ad, As, Pd, and Ps) in each modality.

Results

Psychophysics

Response accuracy in the passive condition was $90.81\% \pm 6.73\%$ and did not differ between non-nociceptive TES and nociceptive IES trials ($p > .05$; $93.12\% \pm 4.51\%$ vs. $89.69\% \pm 6.94\%$). The sensations elicited by the non-nociceptive somatosensory stimuli and nociceptive stimuli were reported as vibratory and pricking, respectively. In the active condition, the average ratings ($\pm SD$) of the sensation elicited by non-nociceptive somatosensory stimuli were as follows: lateral section: 6.13 ± 1.38 ; median section: 6.12 ± 1.26 ; wrist section: 4.77 ± 0.86 . One-way repeated measures ANOVA showed that the ratings were significantly different at diverse stimulation sites, $F(2,42) = 6.57$; $p < .01$. Post hoc analysis revealed that the intensity ratings were significantly lower when the stimuli were

delivered on the wrist section than on the lateral ($p < .01$) and median section ($p < .01$), whereas they were not significantly different when delivered on the lateral versus the median section ($p > .05$). To investigate whether this perceptual difference could be associated to any difference in the electrophysiological patterns, an additional statistical comparison was performed to compare SEP amplitudes obtained from all the hand sections versus amplitudes recorded following only the stimulation of lateral and median sections and omitting the wrist section (no significant difference was found. See online supplementary material for details). The average ratings ($\pm SD$) of the sensation elicited by nociceptive stimuli were as follows: lateral section: 5.80 ± 1.56 ; median section: 5.52 ± 1.01 ; wrist section: 5.93 ± 1.42 . One-way repeated measures ANOVA showed that the intensity ratings were not significantly different among stimulation sites, $F(2,42) = 0.35$; $p > .05$.

Somatosensory Evoked Potentials

Figure 2 (top panel) shows the grand average scalp topographies of SEPs ranging from 80 to 300 ms at four different conditions (Ad, As, Pd, and Ps). All conditions were characterized by a positivity over central-parietal electrodes contralateral to the stimulated body part (i.e., right hand) peaking at around 80 ms, and a negativity on the contralateral central-temporal electrodes peaking at around 120 ms. In addition, a large persisting positivity maximal at frontal-central electrodes was observed between 140 and 300 ms.

Effects of mismatch and attention in SEPs

Spatial regions of interest in SEPs. The factor mismatch significantly modulated SEPs in three distinct sROIs (Figure 2, bottom panel): contralateral temporal region (i.e., FT7, T7, TP7, C5, CP5); ipsilateral temporal region (i.e., T8, TP8); central region (i.e., FC1, FCz, FC2, C1, Cz, C2, CP1, CPz, CP2, P1, Pz, P2). The factor attention significantly modulated SEPs in three distinct sROIs: contralateral temporal region (i.e., T7, TP7, C5, CP5, CP3); ipsilateral temporal region (i.e., C6, TP8); frontal-central region (i.e., F1, Fz, F2, FCz, FC2, C1, Cz, C2).

Temporal regions of interest within each sROI in SEPs. The time course of neural modulations exerted by the factors mismatch and attention within each modulated sROI is represented in Figure 3 (left panel) and Figure 4 (left panel), respectively (cf. Table 1 for details).

Main effect of mismatch. The factor mismatch had a strong modulatory impact on the significant SEP sROIs by exerting a negative amplitude modulation at both contralateral temporal region (SEP-M-tROI¹ a: 110–190 ms; SEP-M-tROI b: 266–382 ms; SEP-M-tROI c: 408–498 ms) and ipsilateral temporal region (SEP-M-tROI d: 162–412 ms), as well as a persisting positive amplitude modulation at central region (SEP-M-tROI e: 94–498 ms). For each tROI, the modulatory effect of mismatch on scalp topography was represented as the difference between response amplitudes obtained in the deviant and standard conditions during both active and passive conditions, according to the formula $[(Ad - As + Pd - Ps)/2]$ (Figure 3, right panel).

Main effect of attention. The factor attention had a similar modulatory impact on the significant SEP sROIs by exerting a

1. SEP-M-tROI: SEP tROI that was significantly modulated by the factor mismatch.

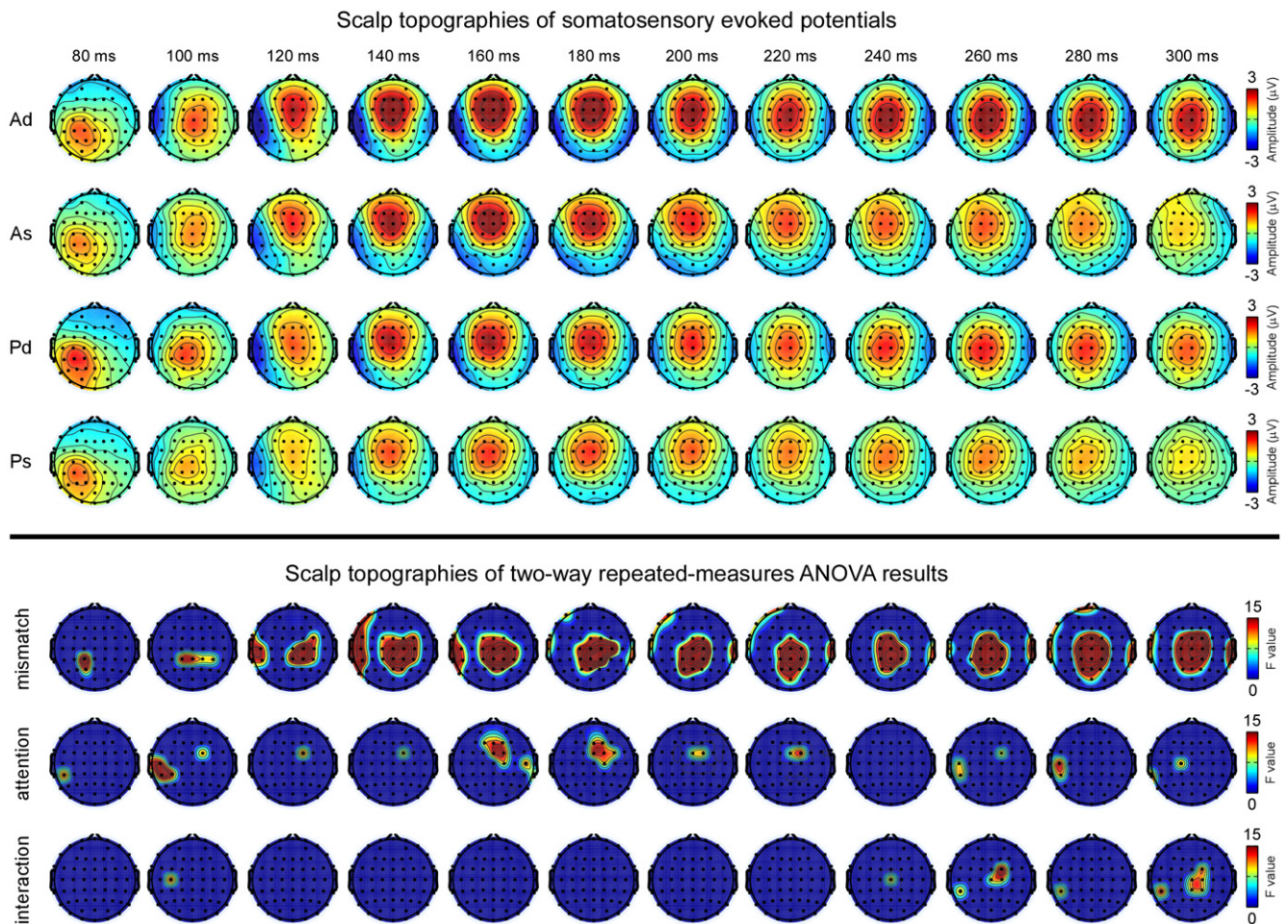


Figure 2. Scalp topographies of SEPs and identification of sROIs. Top panel: Series of 12 scalp topographies of group average SEPs (80–300 ms) at four different conditions (Ad: active-deviant, As: active-standard, Pd: passive-deviant, and Ps: passive-standard) are displayed with a 20-ms interval. Color scale represents amplitude (μV). Note that the scalp topography of the early part of the response displays a contralaterally distributed positivity around 80 ms and a contralaterally distributed negativity around 120 ms (right hand stimulation), whereas the scalp topography of the late part of the response displays a centrally distributed positivity from 140 to 300 ms. Bottom panel: Two-way repeated measures ANOVA to assess the effect of mismatch (deviant vs. standard) and attention (active vs. passive) on SEPs to define significant sROIs. Series of 12 scalp topographies showing each of the factors and their interaction on the SEPs (80–300 ms) are displayed with a 20-ms interval. Color scale corresponds to the *F* value. The factor mismatch significantly modulated SEPs in three distinct sROIs (contralateral temporal region: FT7, T7, TP7, C5, CP5; ipsilateral temporal region: T8, TP8; central region: FC1, FCz, FC2, C1, Cz, C2, CP1, CPz, CP2, P1, Pz, P2). The factor attention significantly modulated SEPs in three distinct sROIs (contralateral temporal region: T7, TP7, C5, CP5, CP3; ipsilateral temporal region: C6, TP8; frontal-central region: F1, Fz, F2, FCz, FC2, C1, Cz, C2).

negative amplitude modulation at both contralateral temporal region (SEP-A-tROI² a: 80–112 ms; SEP-A-tROI b: 248–270 ms) and ipsilateral temporal region (SEP-A-tROI c: 144–172 ms), as well as a positive amplitude modulation at frontal-central region (SEP-A-tROI d: 104–124 ms; SEP-A-tROI e: 144–192 ms; SEP-A-tROI f: 200–224 ms). For each tROI, the modulatory effect of attention on scalp topography was represented as the difference of response amplitudes between active and passive conditions during deviant and standard trials, according to the formula $[(Ad + As - Pd - Ps)/2]$ (Figure 4, right panel).

Interaction of mismatch and attention in mismatch modulated sROIs. Post hoc analysis (Table 2) revealed that SEP amplitudes were significantly larger in Ad than in As ($p < .01$) and Pd

($p < .001$) conditions at the SEP-M-tROI b (266–382 ms). Similarly, SEP amplitudes were significantly larger in As ($p < .001$), Ps ($p < .001$), and Pd ($p < .01$) conditions at the SEP-M-tROI e (94–498 ms). In sum, the two tROIs showed higher amplitudes during the processing of deviant stimuli and when the focus of attention was directed towards the stimulation (Figure 3, top left and right panels).

Noiceptive Evoked Potentials

Figure 5 (top panel) shows the grand average scalp topographies of NEPs ranging from 140 to 360 ms at four different conditions (Ad, As, Pd, and Ps). All conditions were characterized by a negativity on the central-temporal electrodes ranging from 140 to 180 ms and contralateral to the stimulated body part (i.e., left hand), as well as by a large persisting positivity maximal at frontal-central electrodes and ranging from 180 to 360 ms.

2. SEP-A-tROI: SEP tROI that was significantly modulated by the factor attention.

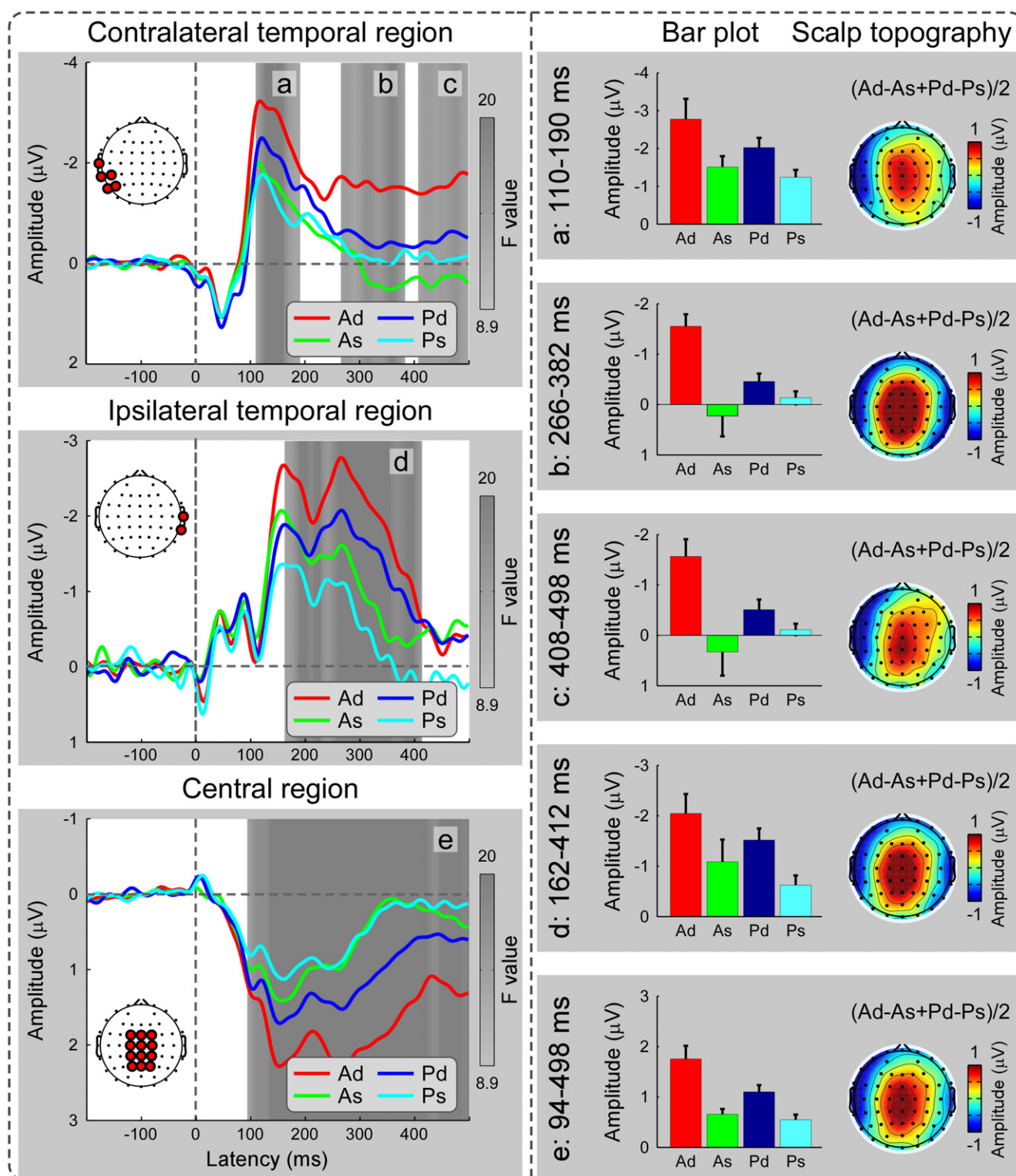


Figure 3. SEPs at the mismatch modulated sROIs. Left panel: In each mismatch modulated sROI, point-by-point, two-way repeated measures ANOVA with the factors mismatch and attention, combined with nonparametric permutation testing, was used to define the mismatch modulated tROIs. x axis, latency (ms); y axis, amplitude (μV). The gray scale represents the F value for the factor mismatch. At the contralateral temporal region, the factor mismatch significantly modulated SEPs in three tROIs (a: 110–190 ms; b: 266–382 ms; c: 408–498 ms). At the ipsilateral temporal region, the factor mismatch significantly modulated SEPs in one tROI (d: 162–412 ms). At the central region, the factor mismatch significantly modulated SEPs in one tROI (e: 94–498 ms). Right panel: In each defined mismatch modulated tROI (a, b, c, d, and e), the amplitudes (mean $\pm$ SEM) across all participants are displayed using bar plots in the left part of this panel, and the corresponding scalp topographies showing the modulatory effect of mismatch $[(\text{Ad} - \text{As} + \text{Pd} - \text{Ps})/2]$ are displayed in the right part of this panel.

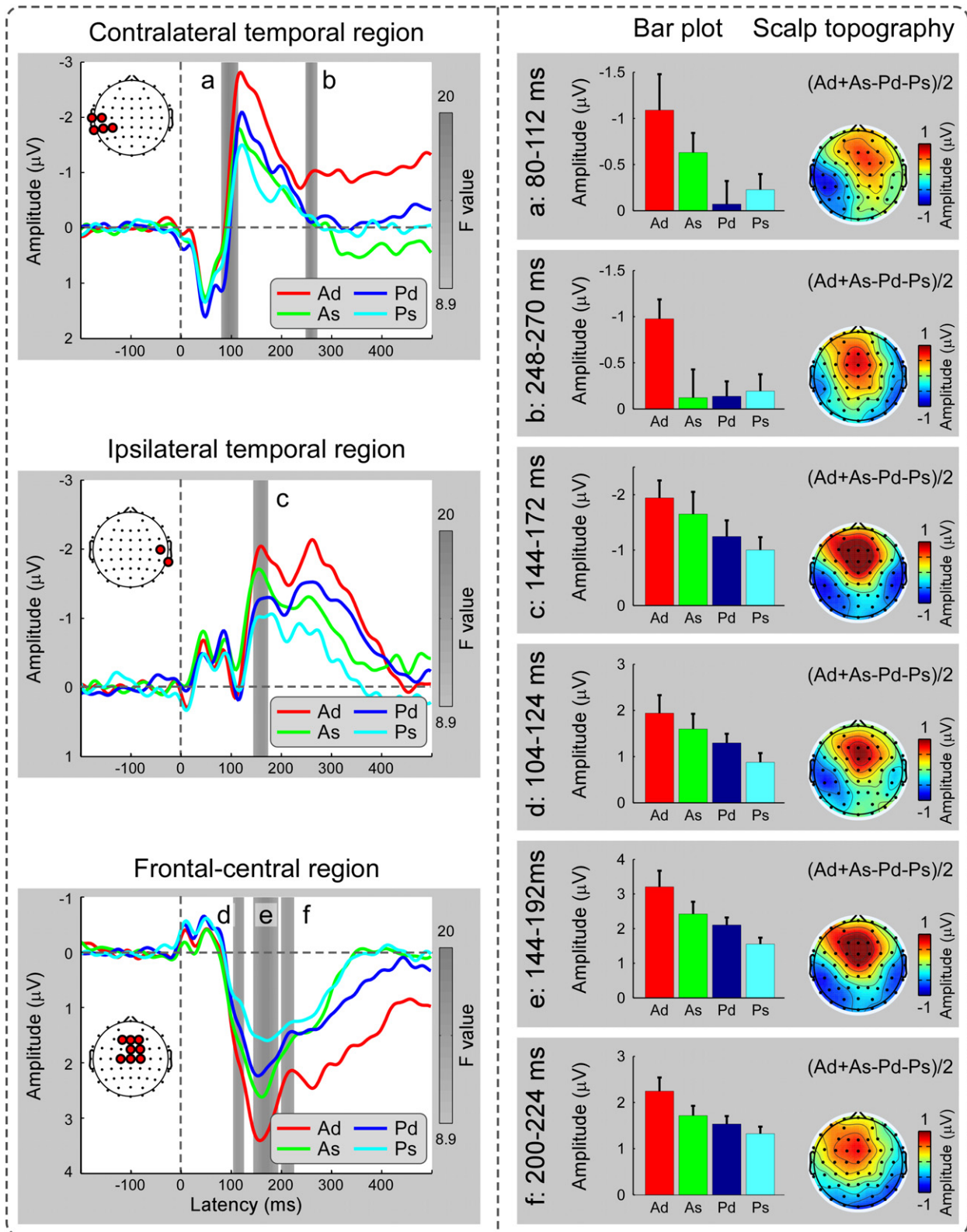


Figure 4. SEPs at the attention modulated sROIs. Left panel: Within each attention modulated sROI, point-by-point, two-way repeated measures ANOVA with the factors mismatch and attention, combined with nonparametric permutation testing, was used to define the attention modulated tROIs. x axis, latency (ms); y axis, amplitude (μV). The gray scale represents the *F* value for the factor attention. At the contralateral temporal region, the factor attention significantly modulated SEPs in two tROIs (a: 80–112 ms; b: 248–270 ms). At the ipsilateral temporal region, the factor attention significantly modulated SEPs in one tROI (c: 144–172 ms). At the frontal-central region, the factor attention significantly modulated SEPs in three tROIs (d: 104–124 ms; e: 144–192 ms; f: 200–224 ms). Right panel: Within each defined attention modulated tROI (a, b, c, d, e, and f), the amplitudes (mean ± SEM) across all participants are displayed using bar plots in the left part of this panel, and the corresponding scalp topographies showing the modulatory effect of attention ((Ad + As – Pd – Ps)/2) are displayed in the right part of this panel.

Table 1. Amplitudes of SEPs and NEPs at Different Experimental Conditions (Ad, As, Pd, and Ps) and ANOVA Results

sROIs	Channels	Label	tROIs (ms)	Ad (μV)		As (μV)		Pd (μV)		Ps (μV)		Main effect of mismatch		Main effect of attention		Interaction	
				Mean ± SE		Mean ± SE		Mean ± SE		Mean ± SE		F	p	F	p	F	p
Mismatch modulation areas of SEPs (Figure 4)	FT7, T7, TP7, C5, CP5 T8, TP8 FC1, FCz, FC2, C1, Cz, C2, CP1, CPz, CP2, P1, Pz, P2	a	110–190	–2.77 ± 0.54	–1.51 ± 0.29	–2.02 ± 0.26	–1.23 ± 0.20	–2.02 ± 0.26	–1.23 ± 0.20	17.93	< .001	4.78	> .01	1.63	> .01	1.63	> .01
		b	266–382	–1.55 ± 0.24	0.22 ± 0.41	–0.45 ± 0.16	–0.13 ± 0.13	–0.45 ± 0.16	–0.13 ± 0.13	13.70	< .01	3.71	> .01	9.86	< .01	9.86	< .01
		c	408–498	–1.56 ± 0.34	0.33 ± 0.47	–0.51 ± 0.20	–0.11 ± 0.13	–0.51 ± 0.20	–0.11 ± 0.13	11.66	< .01	1.28	> .01	4.02	> .01	4.02	> .01
		d	162–412	–2.04 ± 0.39	–1.08 ± 0.44	–1.51 ± 0.23	–0.62 ± 0.20	–1.51 ± 0.23	–0.62 ± 0.20	31.38	< .001	3.13	> .01	0.01	> .01	0.01	> .01
		e	94–498	1.75 ± 0.26	0.65 ± 0.11	1.10 ± 0.14	0.54 ± 0.11	1.10 ± 0.14	0.54 ± 0.11	43.02	< .001	11.07	< .01	8.77	< .01	8.77	< .01
Attention modulation areas of SEPs (Figure 5)	T7, TP7, C5, CP5, CP3 C6, TP8 F1, Fz, F2, FCz, FC2, C1, Cz, C2	a	80–112	–1.09 ± 0.39	–0.63 ± 0.21	–0.07 ± 0.25	–0.23 ± 0.17	–0.07 ± 0.25	–0.23 ± 0.17	0.60	> .01	15.89	< .01	9.92	< .01	9.92	< .01
		b	248–270	–0.98 ± 0.21	–0.12 ± 0.31	–0.14 ± 0.16	–0.19 ± 0.18	–0.14 ± 0.16	–0.19 ± 0.18	2.98	> .01	14.17	< .01	5.87	< .01	5.87	< .01
		c	144–172	–1.94 ± 0.32	–1.65 ± 0.40	–1.24 ± 0.29	–1.00 ± 0.23	–1.24 ± 0.29	–1.00 ± 0.23	3.60	> .01	12.61	< .01	0.02	> .01	0.02	> .01
		d	104–124	1.94 ± 0.39	1.59 ± 0.33	1.29 ± 0.20	0.87 ± 0.20	1.29 ± 0.20	0.87 ± 0.20	5.69	> .01	11.88	< .01	0.14	> .01	0.14	> .01
		e	144–192	3.20 ± 0.47	2.42 ± 0.36	2.10 ± 0.22	1.55 ± 0.19	2.10 ± 0.22	1.55 ± 0.19	14.77	< .01	13.70	< .01	2.00	> .01	2.00	> .01
Mismatch modulation areas of NEPs (Figure 6)	T8, TP8 CP5, P7 FC1, FCz, FC2, C1, Cz, C2, CP1, CPz, CP2 CP6, P6, PO8, P4, PO4	f	200–224	2.24 ± 0.30	1.71 ± 0.21	1.53 ± 0.17	1.32 ± 0.16	1.53 ± 0.17	1.32 ± 0.16	10.15	< .01	10.82	< .01	1.40	> .01	1.40	> .01
		a	182–208	–1.71 ± 0.24	–1.11 ± 0.24	–1.01 ± 0.25	–0.63 ± 0.19	–1.01 ± 0.25	–0.63 ± 0.19	14.07	< .01	5.88	> .01	0.32	> .01	0.32	> .01
		b	246–286	–2.03 ± 0.35	–0.91 ± 0.18	–1.56 ± 0.30	–0.97 ± 0.27	–1.56 ± 0.30	–0.97 ± 0.27	12.68	< .01	0.65	> .01	1.54	> .01	1.54	> .01
		c	186–206	–1.22 ± 0.23	–0.78 ± 0.24	–0.59 ± 0.21	–0.30 ± 0.15	–0.59 ± 0.21	–0.30 ± 0.15	16.59	< .01	7.95	> .01	0.34	> .01	0.34	> .01
		d	224–466	–1.15 ± 0.24	–0.48 ± 0.19	–0.66 ± 0.17	–0.29 ± 0.12	–0.66 ± 0.17	–0.29 ± 0.12	37.07	< .001	2.60	> .01	1.08	> .01	1.08	> .01
Attention modulation areas of NEPs (Figure 7)	T7, TP7, P7 F1, Fz, F2, FC1, FCz, FC2, C1, Cz, C2	e	182–232	1.50 ± 0.27	1.04 ± 0.19	0.78 ± 0.14	0.56 ± 0.13	0.78 ± 0.14	0.56 ± 0.13	17.17	< .001	13.84	< .01	2.03	> .01	2.03	> .01
		f	250–498	1.35 ± 0.13	0.52 ± 0.11	0.70 ± 0.11	0.42 ± 0.09	0.70 ± 0.11	0.42 ± 0.09	38.87	< .001	8.55	< .01	0.88	> .01	0.88	> .01
		a	84–104	–0.47 ± 0.23	–0.32 ± 0.09	0.11 ± 0.14	0.14 ± 0.12	0.11 ± 0.14	0.14 ± 0.12	0.49	> .01	14.73	< .01	1.08	> .01	1.08	> .01
		b	174–204	–0.85 ± 0.25	–0.78 ± 0.17	–0.24 ± 0.15	–0.09 ± 0.14	–0.24 ± 0.15	–0.09 ± 0.14	0.52	> .01	14.10	< .01	0.80	> .01	0.80	> .01
		c	140–230	–1.25 ± 0.26	–0.91 ± 0.28	–0.48 ± 0.19	–0.34 ± 0.15	–0.48 ± 0.19	–0.34 ± 0.15	2.18	< .01	15.41	< .01	0.58	> .01	0.58	> .01
		d	92–114	0.33 ± 0.12	0.22 ± 0.12	–0.09 ± 0.08	–0.12 ± 0.09	–0.09 ± 0.08	–0.12 ± 0.09	0.79	< .01	11.16	< .01	0.18	> .01	0.18	> .01
		e	140–284	1.64 ± 0.27	1.34 ± 0.21	0.91 ± 0.15	0.64 ± 0.14	0.91 ± 0.15	0.64 ± 0.14	10.26	< .01	17.08	< .01	0.06	> .01	0.06	> .01

Table 2. Post Hoc Analysis Using Tukey's HSD Test

sROI	tROI	Ad vs. As <i>p</i>	Pd vs. Ps <i>p</i>	Ad vs. Pd <i>p</i>	As vs. Ps <i>p</i>
Mismatch modulation areas of SEPs (Figure 4)	b	< .01	> .01	< .001	> .01
	e	< .001	< .001	< .01	> .01
Mismatch modulation area of NEPs (Figure 6)	f	< .001	> .01	< .001	> .01

Effect of mismatch and attention in NEPs

Spatial regions of interest in NEPs. The factor mismatch significantly modulated NEPs in three distinct sROIs (Figure 5, bottom panel): contralateral temporal region (i.e., T8, TP8); ipsilateral temporal region (i.e., CP5, P7); central region (i.e., FC1, FCz, FC2, C1, Cz, C2, CP1, CPz, CP2). The factor attention significantly modulated NEPs in three distinct

sROIs: contralateral temporal-parietal region (i.e., C6, P6, PO8, P4, PO4); ipsilateral temporal-parietal region (i.e., T7, TP7, P7); frontal-central region (i.e., F1, Fz, F2, FC1, FCz, FC2, C1, Cz, C2).

Temporal regions of interest in NEPs. The time course of neural modulations exerted by the factors mismatch and attention

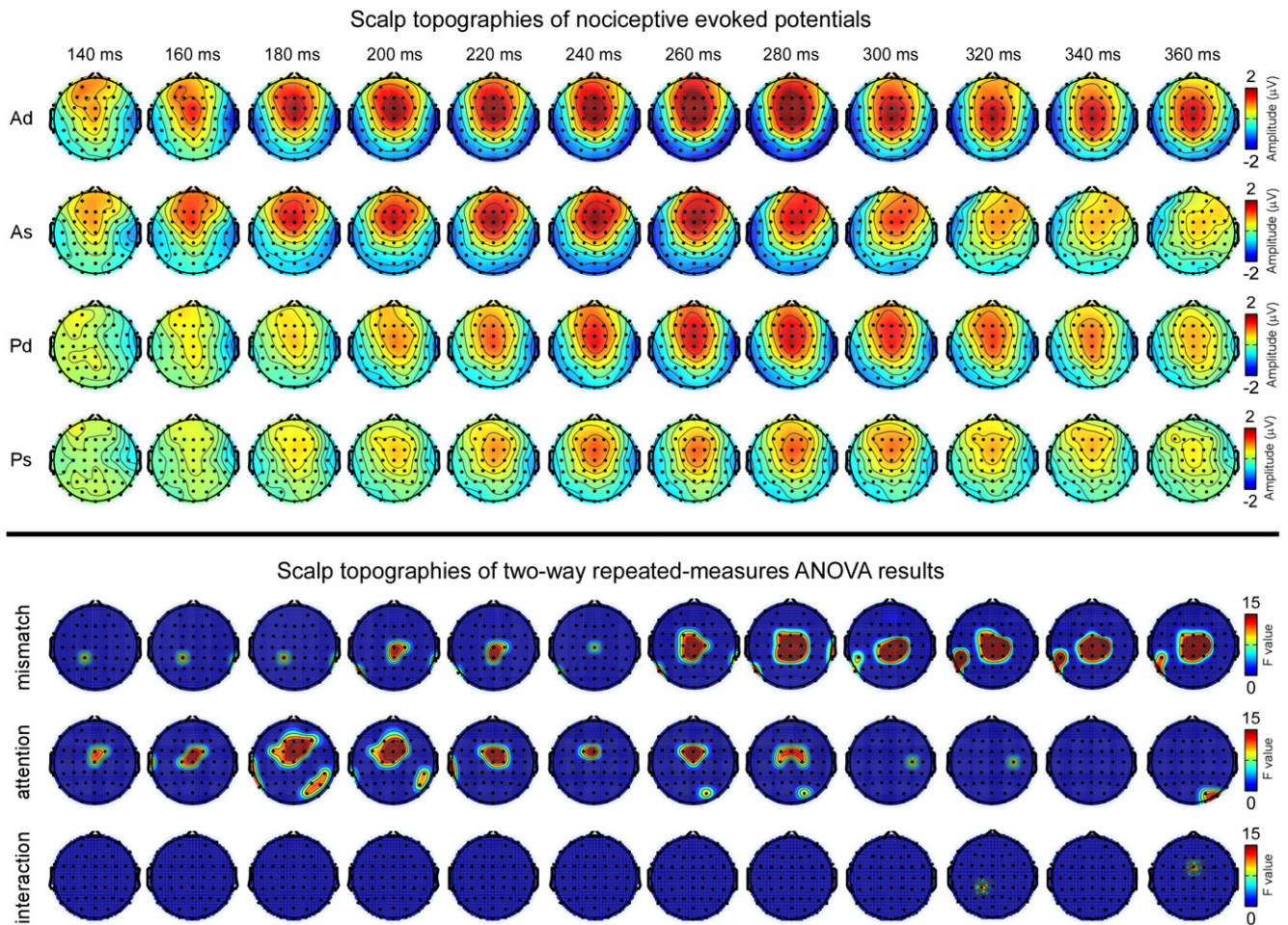


Figure 5. Scalp topographies of NEPs and identification of sROIs. Top panel: Series of 12 scalp topographies of group average NEPs (140–360 ms) at four different conditions (Ad: active-deviant, As: active-standard, Pd: passive-deviant, and Ps: passive-standard) are displayed with a 20-ms interval. Color scale corresponds to amplitude (μV). Note that the scalp topography of the early part of the response displays a contralaterally distributed negativity from 140 to 180 ms (left hand stimulation), whereas the scalp topography of the late part of the response displays a centrally distributed positivity from 180 to 360 ms. Bottom panel: Two-way repeated measures ANOVA to assess the effect of mismatch (deviant vs. standard) and attention (active vs. passive) on NEPs to define significant spatial regions. Series of 12 scalp topographies showing each of the factors and their interaction on NEPs (140–360 ms) are displayed with a 20-ms interval. Color scale corresponds to the *F* value. The factor mismatch significantly modulated NEPs in three distinct sROIs (contralateral temporal region: T8, TP8; ipsilateral temporal region: CP5, P7; central region: FC1, FCz, FC2, C1, Cz, C2, CP1, CPz, CP2). The factor attention significantly modulated NEPs in three distinct sROIs (contralateral temporal-parietal region: C6, P6, PO8, P4, PO4; ipsilateral temporal-parietal region: T7, TP7, P7; frontal-central region: F1, Fz, F2, FC1, FCz, FC2, C1, Cz, C2).

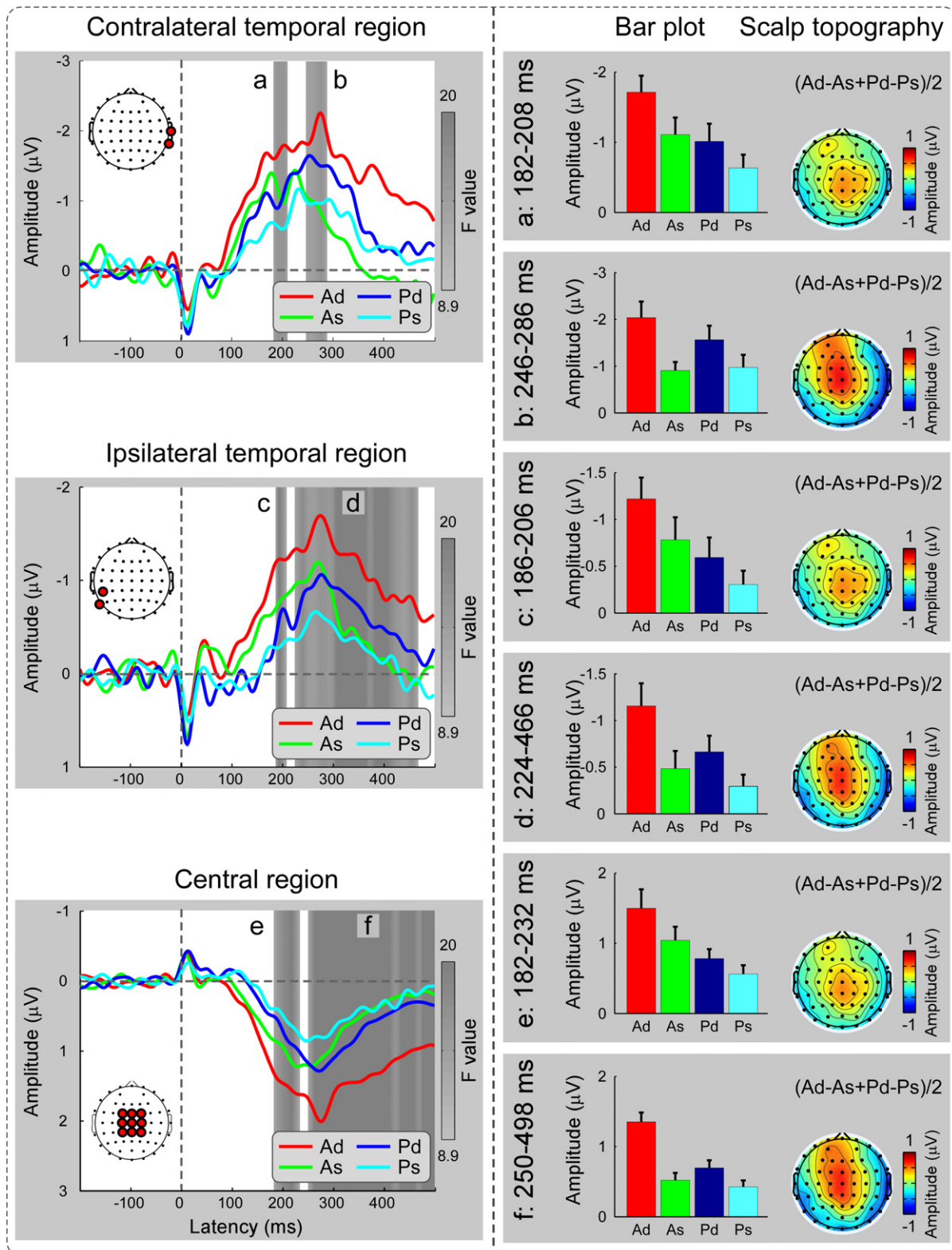
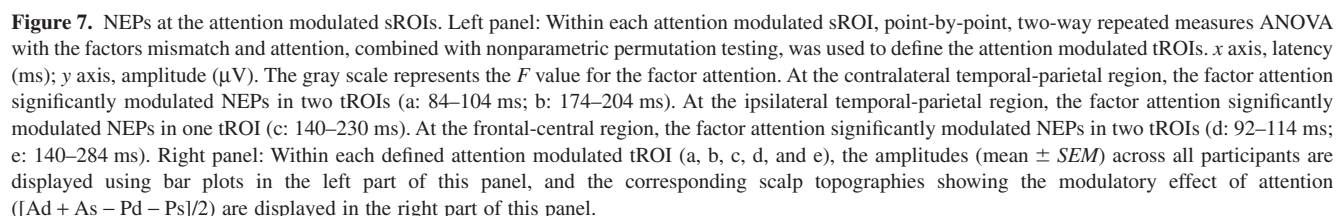


Figure 6. NEPs at the mismatch modulated sROIs. Left panel: Within each mismatch modulated sROI, point-by-point, two-way repeated measures ANOVA with the factors mismatch and attention, combined with nonparametric permutation testing, was used to define the mismatch modulated tROIs. x axis, latency (ms); y axis, amplitude (μV). The gray scale represents the F value for the factor mismatch. At the contralateral temporal region, the factor mismatch significantly modulated NEPs in two tROIs (a: 182–208 ms; b: 246–286 ms). At the ipsilateral temporal region, the factor mismatch significantly modulated NEPs in two tROIs (c: 186–206 ms; d: 224–466 ms). At the central region, the factor mismatch significantly modulated NEPs in two tROIs (e: 182–232 ms; f: 250–498 ms). Right panel: Within each defined mismatch modulated tROI (a, b, c, d, e, and f), the amplitudes (mean $\pm$ SEM) across all participants are displayed using bar plots in the left part of this panel, and the corresponding scalp topographies showing the modulatory effect of attention ($[Ad - As + Pd - Ps]/2$) are displayed in the right part of this panel.



within each modulated sROI is represented in Figure 6 (left panel) and Figure 7 (left panel), respectively (cf. Table 1 for details).

Main effect of mismatch. The factor mismatch had a strong modulatory impact on the significant NEP sROIs by exerting a negative amplitude modulation at both contralateral temporal region (NEP-M-tROI³ a: 182–208 ms; NEP-M-tROI b: 246–286 ms) and ipsilateral temporal region (NEP-M-tROI c: 186–206 ms; NEP-M-tROI d: 224–466 ms), as well as a positive amplitude modulation at central region (NEP-M-tROI e: 182–232 ms; NEP-M-tROI f: 250–498 ms). For each tROI, the modulatory effect of mismatch on scalp topography was represented as the difference between response amplitudes obtained in the deviant and standard conditions during both active and passive conditions, according to the formula $([Ad - As + Pd - Ps]/2)$ (Figure 6, right panel).

Main effect of attention. The factor attention had a similar modulatory impact on the significant NEP sROIs by exerting a negative amplitude modulation at both contralateral temporal-parietal region (NEP-A-tROI⁴ a: 84–104 ms; NEP-A-tROI b: 174–204 ms) and ipsilateral temporal-parietal region (NEP-A-tROI c: 140–230 ms), as well as a positive amplitude modulation at frontal-central region (NEP-A-tROI d: 92–114 ms; NEP-A-tROI e: 140–284 ms). For each tROI, the modulatory effect of attention

on scalp topography was represented as the difference of response amplitudes between active and passive conditions during deviant and standard trials, according to the formula $([Ad + As - Pd - Ps]/2)$ (Figure 7, right panel).

Interaction of mismatch and attention. Post hoc analysis (Table 2) revealed that NEP amplitudes were significantly larger in Ad than in As ($p < .001$) and in Pd ($p < .001$) conditions at the NEP-M-tROI f (250–498 ms). Similar to SEPs, the interaction was explained by higher amplitudes during the processing of deviant stimuli and when the focus of attention was directed towards the stimulation (Figure 6, bottom left and right panels).

The Identification of MMN Activity

The difference waves obtained during the active (Ad-As), rather than passive conditions (Pd-Ps), showed a general increase in signal amplitude for both SEPs and NEPs (Figure 8), especially during the late latencies at central locations (Figure 8, right panel). However, for the purpose of MMN activity identification the pattern of significant tROIs that was statistically affected only by the factor mismatch while being unaffected by the factor attention has been considered. In particular, Figure 8 shows the modulations included in a biologically plausible MMN latency range (100–250 ms) for both SEPs (top panel) and NEPs (bottom panel). As SEP-M-tROIs a (110–190 ms) and d (162–250 ms), as well as NEP-M-tROIs a (182–208 ms), c (186–206 ms), and d (224–250 ms), were located within such latency range, they were identified as candidates of pure automatic preattentive mismatch detection responses.

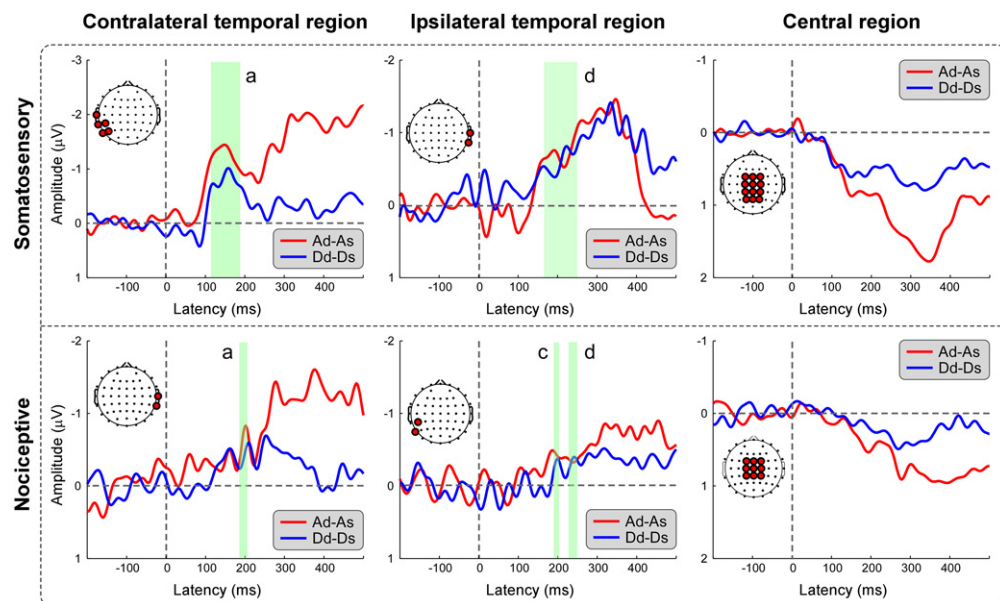


Figure 8. The effect of mismatch as represented by the comparison between active and passive difference waveforms. SEPs elicited by non-nociceptive TES (top) and NEPs elicited by nociceptive IES (bottom) associated to both sROIs and tROIs that were significantly modulated only by the factor mismatch (displayed in Figure 3 and Figure 6, left column), and included in a plausible MMN latency range (100–250 ms, in light green). Importantly, SEP-M-tROIs a and d as well as NEP-M-tROIs a, c, and d were statistically unaffected by attention, and thus can be considered as candidates of pure automatic preattentive mismatch detection. Note how the amplitude of ERP waveforms was increased by directed attention (the comparison between Ad-As and Pd-Ps) to non-nociceptive somatosensory and nociceptive stimuli, particularly for the positivity at late latencies in central region (right panel).

Discussion

Summary of Findings

Here, we aimed to dissect the selective contribution of (a) the effect of a deviant sensory event in a stream of standard events, and (b) the effect of being distracted from such stream of events, in determining the appearance of change detection responses during selective nociceptive stimulation (as compared to somatosensory stimulation), in the context of a roving paradigm (Figure 1).

We observed three main findings. First, the factor mismatch (standard vs. deviant) significantly modulated three distinct sROIs for both SEPs and NEPs (bilateral temporal and central regions). Similarly, the factor attention (active vs. passive) significantly modulated three distinct sROIs (bilateral temporal-parietal and frontal-central regions) for both SEPs and NEPs (Figures 2 and 5, bottom panels). Second, we disclosed the time course of the amplitude modulation exerted by the factors mismatch and attention on each significant sROI. This analysis revealed that both mismatch and attention significantly modulated early and late poststimulus activity elicited by both non-nociceptive TES (Figures 3 and 4) and nociceptive IES (Figures 6 and 7), thus suggesting a high sensitivity of both SEPs and NEPs to the break of regularities, despite the manipulation of the attentional focus. Third, within mismatch modulated sROIs, some tROIs in the expected MMN latency range were modulated by the factor mismatch without being concurrently affected by the factor attention (Figure 8). Altogether, these findings brought about evidence that (a) mismatch brain responses can be elicited by nociceptive stimuli as much as those elicited by non-nociceptive somatosensory stimuli, provided that the effect of attention is accounted for; and (b) these responses are topographically similar but crucially different in their contralateral and ipsilateral onset of activation.

The Effect of Mismatch on SEPs and NEPs

The tROIs identified as sMMN and nMMN were distributed at bilateral temporal regions (Figure 8). Recent studies on somatosensory mismatch brain responses localized the generation of mismatch responses over the contralateral primary and secondary somatosensory cortex (SI and SII) using MEG (Akatsuka et al., 2007). In this regard, it is important to note that one of the main potential generators of the putative sMMN and nMMN, namely SII, is considered to play a role in tactile objective recognition and memory (Seitz, Roland, Bohm, Greitz, & Stone-Elander, 1991).

Importantly, two spatiotemporal features could be appreciated when comparing the significant modulation of sMMN and nMMN (see Figures 3 and 6, left panel, first two graphs from top): (1) The amplitude modulation of the sMMN had an earlier onset than the nMMN both at the contralateral temporal region (SEP-M-tROI a: 110 ms vs. NEP-M-tROI a: 182 ms) and ipsilateral temporal region (SEP-M-tROI d: 162 ms vs. NEP-M-tROI c: 186 ms)—a finding that is fully compatible with the conduction velocity of somatosensory A β and nociceptive A δ fibers (Ploner, Schmitz, Freund, & Schnitzler, 1999, 2000), respectively. (2) The difference of latency between the contralateral and the ipsilateral onset of activity was larger for the sMMN than for the nMMN (52 ms vs. 4 ms), thus supporting the notion that nociceptive processing is faster than tactile processing in the human brain; that is, somatosensory inputs are processed in a serial fashion (e.g., Hu, Zhang, & Hu, 2012) whereas the nociceptive inputs are processed in a parallel manner (Liang, Mouraux, & Iannetti, 2011; Ploner, Gross, Timmermann, & Schnitzler, 2006; Ploner, Schoffelen, Schnitzler, & Gross, 2009).

Crucially, as the topographies of these responses largely overlapped, latency discrepancies are the main salient differences between sMMN and nMMN.

The Effect of Attention on SEPs and NEPs

The impact of attention on SEPs and NEPs had no less importance than the factor mismatch in determining amplitude modulations. As observed in previous studies, active attention enhanced event-related potential (ERP) amplitudes related to passive shifts of attention to somatosensory stimuli (Kida, Nishihira, Wasaka, Nakata, & Sakamoto, 2004a, 2004b; Kida, Wasaka, Nakata, Akatsuka, & Kakigi, 2006). Noteworthy is that, while part of the negative activity at bilateral temporal regions resembled the activity associated to the mismatch-related modulation, its vertex positive counterpart was distributed at frontal-central electrodes (maximal at FCz, Figures 4 and 7, right panels) rather than at central sites (maximal at Cz, Figures 3 and 6, right panels), as result of the effect of attention. The allocation of attention may trigger the activation of medial structures, such as different portions of the anterior and mid cingulate cortex, which is widely acknowledged as one of the most important areas responsible for the allocation of voluntary and involuntary attention, regardless of the sensory modality used in the experimental task (e.g., see Legrain, Iannetti, Plaghki, & Mouraux, 2011, for a review).

It is worth noting that a prefrontal activation was reported by the original study of somatosensory mismatch responses (Kekoni et al., 1997). This generator was observed in auditory mismatch studies as well, and interpreted as the source of a top-down modulation of the deviance detection system in the temporal cortices (e.g., Doeller et al., 2003). However, contrary to the literature on auditory mismatch responses, it is still unclear which central and frontal structures may be involved in somatosensory change detection responses.

The present findings hint of a potential difference in the amount of structures recruited during SEPs versus NEPs. In particular, SEPs were associated to larger mismatch modulated sROIs than NEPs, whereas NEPs were coupled to larger attention modulated sROIs than SEPs (Figures 2–7). This observation may suggest an important functional difference between nociceptive and somatosensory change detection responses, associated to voluntary and involuntary attentional gains. This notion is consistent with the general consensus on the ability of pain to grab attention *per se* (Seminowicz & Davis, 2007; Wiech, Ploner, & Tracey, 2008).

Methodological Considerations

A crucial methodological aspect of this study rests on the application of intraepidermal electrodes to preferentially stimulate skin nociceptors (Inui et al., 2002, 2006). The IES allowed us to implement a roving paradigm, whereby deviants and standards had exactly the same number of trials and physical properties. This procedure ensured that standards were really perceived as standards, and that the only difference between deviants and standards was associated to their position in the train (i.e., deviant first, standard last). Conversely, radiant heat stimulators such as Nd: YAP (neodymium-doped yttrium aluminum perovskite) and CO₂ laser stimulators, although widely used to selectively activate nociceptive A δ fibers, are affected by a few important limitations, which prevented their application in the present context. First, radiant heat stimulators require the delivery of each single thermal pulse either at long ISIs (at least 5 to 10 s) and/or at different spatial locations after each trial,

to avoid skin overheating, nociceptors fatigue, and/or sensitization (Plaghki & Mouraux, 2003). This technical aspect is clearly incompatible with the requirements of a roving paradigm (or similar oddball paradigm used to elicit a MMN). In fact, both long ISIs and the displacement of each single sensory event would have hampered the creation of real standard events, due to their inner disparity in time and space. Second, currently available laser stimulators do not allow online skin temperature control, which changes independently from the physical properties of the impending stimuli (Plaghki & Mouraux, 2003). Altogether, these reasons concurred to prove that IES was the most effective way to determine the identification of a possible nMMN.

A second methodological aspect of the present study concerns the experimental design. An important characteristic of the MMN generation in classic auditory oddball paradigms rests in the possibility to detect this ERP component when the participant is not paying attention to the sensory event, as compared with a condition of active attention. However, many studies simply did not include a condition whereby the participant is required to attend to the sensory event, thus assuming that the sole condition of inattention would suffice showing the MMN phenomenon (Sussman, 2007). Unfortunately, this methodological flaw applies to most previous somatosensory change detection studies as well (e.g., Kekoni et al., 1997; Shinozaki, Yabe, Sutoh, Hiruma, & Kaneko, 1998). It is worth noting that the majority of studies investigating the MMN phenomenon assumed that watching a silent video with subtitles while ignoring the sensory test stimulation is the best means to obtain a mismatch response. However, other authors have put forth that the MMN elicited under these conditions may not be an attention-independent measure because these tasks do not require highly focused attention (Haroush, Hochstein, & Deouell, 2010). Conversely, asking the subject to disregard the sensory test stimulation (e.g., auditory) while focusing on a concurrent demanding task (e.g., detection of visual stimuli) should provide a better characterization of the MMN response. In the present experiment, participants were asked to report details and plots related to the movie watched during the passive condition, thus requiring them to deploy attention. Nevertheless, an “active distraction” associated to a high attentional load exerted by a visual search task could be implemented by future studies on nMMN, to further detail the methodological constraints of this phenomenon.

A last methodological issue requires the reader's attention. Somatosensory and nociceptive afferents have different conduction pathways (Ploner et al., 1999, 2000). This feature makes difficult any direct quantitative comparison between sMMN and nMMN, as both latencies and amplitudes would be intrinsically different regardless of the experimental manipulation, and such difference would in turn affect the partitioning of variance and its attribution to a given experimental condition (this would apply to a direct quantitative comparison of auditory and

visual MMN as well). Thus, our experimental investigation implied a qualitative comparison of the sMMN and nMMN latency profiles.

Theoretical Considerations

On the basis of the current results, we speculate that the identified modulations may represent an index of automatic detection of nociceptive change. Yet, the present experiment does not allow us to answer whether the purported mismatch responses may rely only on sensory memory mechanisms (Naatanen, Paavilainen, Rinne, & Alho, 2007) or whether they are contributed by neural refractoriness and lateral inhibition mechanisms (May & Tiitinen, 2010). Interestingly, previous research in the domain of cortical responses elicited by repeated nociceptive stimuli of identical energy (Iannetti, Hughes, Lee, & Mouraux, 2008; Wang, Mouraux, Liang, & Iannetti, 2010) seems to support the notion that the suppression of nociceptive-related ERPs are strongly determined by the novelty (as a function of saliency) of the eliciting stimulus (Valentini, Torta, Mouraux, & Iannetti, 2011; Wang et al., 2010), rather than by neural refractoriness per se (Truini, Galeotti, Cruccu, & Garcia-Larrea, 2007; Truini et al., 2004). However, contemporary research in the field of auditory MMN increasingly put forth the idea that neural adaptation and sensory memory may be reconciled within the predictive coding framework (Garrido, Kilner, Stephan, & Friston, 2009). According to this account, the MMN represents a failure to suppress prediction error when novel and rare stimuli are presented once a generative model of the standards was established. It is claimed that the predictive coding theory may account both for the adjustment of a mnemonic model of the ongoing stimulus trains (i.e., the model-adjustment hypothesis; Naatanen & Winkler, 1999) and for the local changes in postsynaptic sensitivity (i.e., adaptation hypothesis; Jaaskelainen et al., 2011), likely contributing to perceptual learning. Interestingly, a recent study proposed a neuronal model of MMN generation in the auditory cortex based on the predictive coding features, without any additional assumption associated to synaptic habituation (Wacongne, Changeux, & Dehaene, 2012). This model was able to account for several empirical properties of MMN such as frequency-dependent response to rare deviants and response to unexpected repetitions in alternating sensory events. We agree with the authors of this study that these findings provide strong evidence in support of the notion that the MMN phenomenon can be interpreted as an index of novelty detection while arguing against a strong contribution of neural refractoriness, and thus strengthening the notion of a purely predictive account of MMN regardless of neural refractoriness.

In conclusion, the MMN has been advocated as a tool for assessing abnormal brain function in a large number of clinical conditions, except that of chronic pain conditions (Naatanen et al., 2011). Further research effort is therefore mandatory to disclose the extent of this phenomenon in nociceptive-related ERPs.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Appendix S1: This section provides further information about the comparison of SEP amplitudes obtained from all the hand sections (L, M, and W) and amplitudes from two sections (L and M).

Figure S1: Comparison of SEPs amplitudes elicited by stimuli delivered either from three sections (L, M, and W) or from two sections (L and M).