



# Endogenous spatial attention directed to intracutaneous electrical stimuli on the forearms involves an external reference frame



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## ABSTRACT

In the present study, we examined whether the direction of attention while anticipating intracutaneous electrical stimuli on the left or right forearm occurs within an internal somatotopic or an external body-based reference frame. Participants placed their hands on a table in front of them in a normal position or in a crossed-hands position. A symbolic cue with a validity of 80% instructed participants to attend to either the left or the right side, which varied from trial to trial. Crossing the hands induces a conflict of internal and external reference frames which allows to determine the dominating reference frame(s). Analyses of the electroencephalogram (EEG) during the orienting phase revealed that crossing the arms did not induce a reversal of neural activity over central sites as a late direction attention-related positivity and increased ipsilateral alpha power over occipital and central sites was observed in both conditions. Hand position influenced the processing of the electrical stimuli as no effect of cue validity was observed on the P3a component in the crossed-hands position. Our results indicate that endogenous spatial attention to intracutaneous electrical stimuli primarily occurs within an external reference frame.

## 1. Introduction

Healthy humans have a number of important automated actions and mechanisms on their repertoire to ensure their survival. The ability to sense pain enables us to cope with potential life-threatening events. In such conditions, the sensation of pain triggers the orientation of attention (i.e., exogenous orienting; Eccleston and Crombez, 1999), which facilitates the selection of actions to adequately deal with the potential life-threatening situation. The mechanisms underlying this direction of attention to a location on the body in response to a painful event or while anticipating such an event are not yet fully understood. However, several recent studies with human participants indicate that the influence of painful events may be substantially reduced when attention is directed elsewhere (e.g., see Legrain et al., 2002; Van der Lubbe et al., 2012b, 2017) or in the case of distraction by a secondary task such as mental arithmetic or a word-association task (e.g., see Blom et al., 2012). A better understanding of the orientation of attention while expecting pain and in response to painful stimuli, could be an important starting point for the development of new and more effective behavioral therapies for patients suffering from (chronic) pain.

The voluntary direction of attention to a certain location (i.e., endogenous orienting) may in principle be carried out within multiple

spatial reference frames (e.g., see Avillac et al., 2005). Spatial locations are encoded differently when the reference frames refer to different reference points. This is obvious when one considers spatial coding for different modalities. For example, the position of a word on a screen in front of you will be anchored to the retina; a sound emitted from the same location will be coded relative to the orientation of your head; a key press will be related to the orientation of your body and the relevant hand; and a wasp on your arm trying to sting you concerns a location on your body related to the surface of your skin. Thus, spatial references may have retinal, head-centered, body-centered, hand-centered, and somatotopic reference points. The general idea is that somewhere in the brain these different reference frames are integrated, although according to Avillac et al. (2005) this only occurs to some extent, as bimodal neurons were observed in parietal cortex of the macaque that respond to visual and tactile stimuli within different reference frames. Interestingly, McCloskey and Rapp (2000) argued that a crucial reference point may be attention itself as the instruction to attend to a certain location had a major influence on the type of errors made by a patient with a developmental deficit in localizing visual stimuli. Studies with the Simon effect (see Abrahamse and Van der Lubbe, 2008; Van der Lubbe and Abrahamse, 2011; Van der Lubbe et al., 2012a, 2012b) also point to a crucial role of attention in spatial

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coding. Van der Lubbe et al. (2012a, 2012b) proposed that attention operates within a supramodal spatial map within parietal cortex that integrates different input and output modalities (see also Astafiev et al., 2003). This supramodal map may correspond with our phenomenological experience of space as we experience a stable world when we are making head or eye movements and also when we are moving through space (e.g., see Van der Heijden, 2004).

The location of a painful event on the forearm and attending to this event may thus be defined within different reference frames. Here, we will restrict us to definitions within a somatotopic (or internally) based reference frame, and a body-centered (or external) reference frame. Within the internal reference frame the spatial code of the event is independent of the position of a relevant body part (e.g., the arm) in external space, while within an external reference frame the spatial code depends on the position of the relevant body part in external space. This often depends on a visual representation of external space and the location of the body part within that space. The question may be raised within what reference frame attention operates when it is directed to the likely body part at which a painful stimulus may be presented. This could be an internal reference frame, an external visually-based reference frame, but it may also concern a combination of the two. A combination of both reference frames may be more likely as recent studies revealed that a stimulus applied to a body limb modifies processing of a visual stimulus delivered closely to that limb (see Favril et al., 2014). The latter observation also accords with the earlier suggestion that attention operates within a supramodal spatial map (see also Driver and Spence, 1998; Van der Lubbe and Postma, 2005; Van der Lubbe et al., 2010).

In order to determine what reference frame (internal or external) is dominant while attending to a location on the body a crossed-hands manipulation may be employed. When the hands are placed in a normal position (i.e., left hand on the left side and vice versa) the guidance of attention via either of the reference frames will correspond. However, when the hands are crossed over the body midline (i.e., the left hand is now placed on the right side and the right hand is located on the left side) a conflict between the two reference frames may be induced. Namely, when attention is guided by an internal or somatotopic reference frame to the left hand, this should lead to a change in activity in the right hemisphere, as the neural activity representing the direction of attention to the body part is independent of the location of the hand in space. In contrast, when attention is directed to the left hand placed on the right via an external reference frame, activity would be modified in the left hemisphere. Thus, if activity stays the same in normal and crossed-hands positions this supports the involvement of an external reference, while an inversion of activity in the crossed-hands position would support the involvement of an internal reference frame. In the case of delivery of painful stimuli to the hands, using a normal or a crossed-hands position should also allow to determine the major involvement of an internal or an external reference frame. When the direction of attention occurs primarily within an internal reference frame a reversal of activity should be observed relative to the normal position condition (e.g., see Gherrri and Forster, 2012), as then hand-related (and possibly attention-related) neural activity has an ipsilateral focus (relative to the attended location). Absence of a reversal of activity in the crossed-hands condition would support the involvement of an external reference frame.

A suitable task to study endogenous orienting and examine the involvement of different spatial reference frames is a variant of the Posner paradigm (Posner et al., 1980; Van der Lubbe et al., 2006). In this paradigm, a centrally presented visual cue is used to indicate the location (left or right) to which attention has to be directed in anticipation of a relevant stimulus, which enables to study the orienting phase. In one version of this paradigm (also employed here), the cue indicates the location of a target with a certain validity (e.g., 80%), implying that on invalidly cued trials, the target is presented at the uncued location. The common observation is that validly cued targets are followed by

faster and more accurate responses than invalidly cued targets, which demonstrates the influence of attention at a behavioral level (e.g., see Van der Lubbe et al., 2006). Other versions of this paradigm have been used in which the cue is mandatory, implying that responses should only be made concerning stimuli at attended and not at unattended locations (e.g., see Van der Lubbe et al., 2012a, 2012b, 2017).

The neural activity reflecting the direction of endogenous spatial attention in the orienting phase can be examined by calculating event related lateralizations (ERL) on the basis of direction-dependent event related potentials (ERPs), which can be derived from the electroencephalogram (EEG). The advantage of ERLs is that they display the neural activity that solely depends on the direction of attention. ERLs can be computed by determining contra-ipsilateral difference waves for left and right relevant sides, and subsequently average them (a so-called double subtraction technique applied to symmetrical electrode sites, which was introduced by Wascher and Wauschkuhn, 1996). ERLs in the orienting phase generally display a number of components that are thought to reflect different stages of attentional orienting. An early contralateral negativity over occipito-parietal sites observed around 200–400 ms after cue onset, the early directing attention negativity (EDAN), is thought to reflect the selection and interpretation of the lateral relevant part of the cue (see Van Velzen and Eimer, 2003). The later anterior directing attention negativity (ADAN) is often observed over anterior sites at around 400 ms after cue onset, and is suggested to reflect the control of spatial attention that affects subsequent posterior processes (e.g., see Grent-t-Jong and Woldorff, 2007; for an alternative view, see Van der Lubbe et al., 2006). Finally, a late directing attention positivity (LDAP) is generally observed over posterior sites around 500–700 ms after cue onset, which is thought to reflect spatial selection processing based on a body-centered reference frame (Hopf and Mangun, 2000; Gherrri et al., 2007).

In a recent study with tactile stimuli (Gherrri and Forster, 2012), participants were instructed to attend to the hand placed on the side indicated by a visual cue and to respond whenever a target tactile stimulus was presented at the cued hand. Non-target stimuli (both at the cued and the uncued hand) had to be ignored. On half of the trials the hands were to be placed in a crossed-hands position, which was varied between blocks. ERLs were computed to examine the orientation of attention. Results revealed an LDAP over posterior sites contralateral to the cued side in space, regardless of the hand position. An ADAN was observed over fronto-central electrodes between 300 and 500 ms post-cue. This component was also unaffected by the hand position. Hence, based on these results it seems that covert shifts of attention are exclusively guided by an external reference frame. Later in the cue-stimulus interval (700–900 ms time-interval) an enhanced negativity was observed over central sites, which reversed in polarity on crossed-hands conditions. Thus, the component was observed contralateral to the relevant hand and not contralateral to the cued side of space, which suggests that it reflects a process that takes place within an internal reference frame.

The ERL method is based on evoked activity (activity is time-locked and phase-locked to a certain event), which implies that individual differences and especially intra-individual differences (trial-to-trial fluctuations) are cancelled out (e.g., see Van der Lubbe et al., 2014, 2017). Recently, Van der Lubbe and Utzerath (2013) introduced a method, which enables to assess lateralized activity that is not strictly phase-locked to a specific event. In this method, the lateralized power of the EEG is determined for different frequency bands (i.e., lateralized power spectra [LPS]) by means of a double subtraction technique. Activity in the alpha frequency band, ranging from 8 to 13 Hz, is thought to reflect inhibition of task-irrelevant processes, which may lead to an enhanced signal-to-noise ratio. The often observed ipsilateral increase in alpha power suggests that processing of the irrelevant as compared to the relevant field is suppressed. Alpha activity predominantly originates from occipital sites (Klimesch et al., 2007) and is therefore primarily associated with (visuo-)spatial processes. An increase in posterior

ipsilateral alpha activity over occipital sites independent from hand position would suggest that attention is directed along an external reference frame. Above central sites (overlying primary motor and somatosensory cortex), lateralized activity can be observed within the same frequency band, which is generally denoted as “mu” activity. Mu power also decreases in the case of cortical involvement, with movement or just an intention to move (e.g., Pfurtscheller et al., 1997). If attention affects somatotopic activity (e.g., see Anderson and Ding, 2011) then a reversal of activity (both ERLs and lateralized mu power) should be observed in the case of a crossed-hands position relative to when the hands in a normal position (see, Eimer et al., 2002, 2003, 2004; Gherri and Forster, 2012). In contrast, if attentional orienting occurs within an external reference frame, then no effect of hand position should be observed on ERL components or lateralized alpha or mu power.

Several earlier studies examined the orienting phase while awaiting tactile stimuli (see, Eimer et al., 2002, 2003, 2004; Gherri et al., 2007; Gherri and Forster, 2012), however, it may be questioned whether a similar strategy is employed while anticipating painful stimuli. First, painful stimuli are likely to have a larger impact on attentional orienting due to their crucial role in signaling potential life-threatening damage to the body (Eccleston and Crombez, 1999). If we become aware of a wasp on our right foot that is laying on the left and anticipate a bite, then it may be more relevant to locate this wasp in external space than in internal space as we intend to get rid of the wasp, on the other hand the anticipated bite will still occur within a somatotopic internal reference frame. Secondly, the anatomical and neural processing of tactile and painful stimuli is not identical. Specifically, tactile stimuli are processed along A $\beta$ -fibers with a speed of 30 to 70 m/s (Millan, 1999; Manzano et al., 2008). Painful stimuli that selectively activate pain receptors in the skin, however, are processed along much slower pain-specific (nociceptive) fibers (A $\delta$ - and C-fibers) with a speed of 2 to 30 m/s (Millan, 1999; Manzano et al., 2008). Nociceptive fibers cross to the contralateral side directly after entering the dorsal root ganglion cells in the spinal cord, while tactile fibers initially stay on the ipsilateral side. Both paths join at the level of the medulla and project to the ventral posterior medial nucleus of the thalamus, thereafter they reach the primary somatosensory cortex (e.g., see Purves et al., 1997). Given these different processing routes, the different arrival times in primary somatosensory cortex, and the aforementioned functional differences it may very well be the case that attentional modulation differs between tactile and painful stimuli.

We employed a variant of the Posner paradigm to examine the influence of endogenous orienting on the processing of intracutaneous electrical stimuli. We examined both the orienting phase and the subsequent processing of the anticipated stimuli. The employed stimulation technique determines which fibers are activated. Whereas transcutaneous electrical stimulation has been shown to activate tactile fibers (A $\beta$ -fibers) besides pain specific fibers (A $\delta$ -fibers and C-fibers), intracutaneous electrical stimuli more selectively activate A $\delta$ -fibers (Mouraux et al., 2010; Steenbergen et al., 2012; Legrain and Mouraux, 2013). The neural processing in response to the intracutaneous electrical stimuli can be examined by computing ERPs.

Earlier studies employing tactile stimuli and crossed-hands manipulations reported that the amplitude of the N1 component was delayed and attenuated in crossed-hands conditions, which seems to be the result of a mismatch between internal and external reference frames (e.g., see Eimer et al., 2001). Other studies employing attention manipulations to examine the effect of attention on stimulus processing revealed larger amplitudes of the N1 components whenever attention was directed at the location of the stimulus, while increased amplitudes of the P3a component were observed in response to unattended stimuli (see Van der Lubbe et al., 2012b, 2017). If exogenous orienting effects induced by the intracutaneous electrical stimuli completely overrule the earlier orienting after the cue, then no effects of cue validity and hand position and no interaction between cue validity and hand position

should be observed on the N1 and P3a components. In contrast, presence of a cue validity effect on normal hand position trials but absence of a cue validity effect on crossed hands trials would indicate that exogenous orienting effects are modulated by the allocation of attention to the location of the arm, which implies that endogenous orienting does not operate within an internal reference frame. Finally, presence of a cue validity effect irrespective from hand position would support the idea that endogenous orienting occurred within an internal reference frame.

## 2. Methods

### 2.1. Participants

Sixteen healthy students (6 males and 10 females, age: 19–27 years) participated in this experiment, which lasted approximately 3 h. Handedness was assessed with the Annett Handedness Inventory (Annett, 1970). Fifteen participants were right-handed, whereas one participant was ambidextrous. All participants had normal or corrected-to-normal vision and were free of neurological and psychiatric illness. Every participant received a detailed explanation of the procedure and signed a written informed consent before participating. They received €18 for their participation. The Medical Ethical Committee of Medisch Spectrum Twente, Enschede, The Netherlands, approved the employed experimental procedures (NL31474.044.11/P11-11).

### 2.2. Electrical stimuli and procedure

Intracutaneous electrical stimuli were generated by two DS5 constant current stimulators (Digitimer, Welwyn Garden City, UK). Bipolar concentric electrodes (Inui et al., 2002) were positioned above the median nerves of the left and the right forearms to deliver the stimuli. These bipolar concentric electrodes use a short needle, which slightly penetrates the epidermis to selectively activate the A $\delta$ -fibers (see Mouraux et al., 2010). Stimuli of two intensity levels were used with a fixed intensity of the stimulus current that matched the individual participant's thresholds (see below). The low intensity stimuli consisted of a volley of two 1 ms rectangular pulses and the high intensity stimuli consisted of a volley of five 1 ms rectangular pulses. The interpulse interval between two subsequent pulses in the pulse train was 5 ms, which lies well outside the neuronal refractory period. This was done to control for possible temporal summation of pulses in a longer train (Van der Heide et al., 2009).

A pretest was used to assess the stimulus current intensities matching the participant's individual sensation threshold, pain threshold, and pain tolerance level. Thresholds were identified by increasing the current of a five-pulse stimulus with steps of 0.1 mA starting from zero. Participants were instructed to report the first stimulus that they were able to detect (sensation threshold,  $M = 0.3$  mA;  $SE 0.03$ ).<sup>1</sup> With increasing current amplitudes, the character of the stimulus changes from a small pinprick sensation to a painful prickling sensation (pain threshold ( $M = 0.9$  mA;  $SE 0.3$ )). Increasing the intensity of the current even further causes the sensation to become unpleasant, corresponding to the pain tolerance level ( $M = 1.2$  mA;  $SE 0.2$ ). The amplitude of the stimulus current used during the experiment was set at this last threshold level.

Five stimulus-rating sessions were used during the experiment. The first session took part before the first block and the other sessions were presented after each of the four blocks. The sensation ratings were used to control for possible hypervigilance or habituation, which could occur

<sup>1</sup> The observed sensation threshold in the current study is substantially higher than in the study of Mouraux et al. (2010), where they report a threshold of 0.08 mA. These differences may be due to details in the followed procedures, the employed apparatus, and the involved participants.

due to repeated stimulation. During each session one two-pulse stimulus and one five-pulse stimulus was presented to the participant at the left and right forearm in a random order. The participants were asked to rate each stimulus separately on a digital Visual Analogue Scale (VAS), which was displayed on the screen 1000 ms after stimulus onset. Participants were asked to rate the stimulus intensities on a 0–10 scale using the left and right arrows on a keyboard. Zero on the VAS matched to 'no feeling at all' whereas 10 matched to 'extremely painful'. The hands of the participant were always in a normal uncrossed position during the stimulus-rating sessions. The rating sessions were followed by a 2-minute break.

### 2.3. Task and stimuli

The experiment started with a short explanation of the purpose of the task, which was presented on the participant's screen. The task started after the thresholds pretest, a VAS stimulus-rating session, and a short practice block containing 16 trials. A total of four blocks, each containing 100 trials, was presented. In two blocks (the first and third block, or the second and the fourth block) participants were instructed to cross their arms (right over left) and to lay their hands on the same location on the table. Thus, the order of the normal and crossed-hands blocks was counterbalanced across participants. The distance between the left and right hands was about 30 cm in both conditions.

A white fixation cross was displayed throughout a trial. Twelve hundred millisecond after trial onset the cross was replaced by a visual cue (a rhomb) for 400 ms. The cue consisted of a red and a blue triangle both pointing outwards (◀▶ or ▶◀). The cue signaled the likely target side of an upcoming stimulus by the direction of the red or the blue triangle. The order of the relevant color (the first and second block red, and the third and fourth block blue, or vice versa) was also counterbalanced between participants. The relevant side of the rhomb pointed with equal probability to the left or the right side. On 80% of the trials the cued target side was correct (validly cued trials) and on the other 20% of the trials the direction of the cue was incorrect (invalidly cued trials). Six hundred millisecond after offset of the rhomb a low or a high intensity electrical stimulus was delivered at the participant's left or right forearm. Half of the stimuli were of low intensity (two-pulse stimuli) and the other half of the stimuli were of a high intensity (five-pulse stimuli). Participants were instructed to report if the delivered stimulus had a low or a high intensity by pressing either the left or the right foot pedal with respectively their left or right foot. Responses were instructed to be as fast and accurately as possible after stimulus onset. The white fixation cross subsequently turned grey as an indication that a response was made. Only during the first sixteen practice trials the fixation cross would turn green or red informing the participant about the correctness of their responses. No feedback on performance for individual trials was given in the four test blocks. However, a general performance indication was provided after each block. The required response side for low and high intensity stimuli was additionally counterbalanced between participants. A trial ended 4000 ms after the onset of the electrical stimulus.

### 2.4. Recordings

EEG was recorded from 61 standard electrode positions (the extended 10–20 system), using passive Ag/AgCl electrodes mounted on an electrocap (EasyCap GmbH, Hirsching-Breitbrunn, Germany). All electrode impedances were reduced until below 10 k $\Omega$ . A ground electrode was placed on the forehead. The vertical and horizontal electrooculogram (EOG) were measured with bipolar Ag/AgCl electrodes located on the outer canthi of the eyes and from above and below the left eye. Signals passed through a QuickAmp amplifier (Brain Products GmbH, Munich, Germany) and were recorded online against an average reference at a sample rate of 500 Hz. Online filtering with a 200 Hz low pass filter and a notch filter of 50 Hz was applied

throughout the recording session.

### 2.5. Data analyses

Stimulus intensity ratings assessed with the VAS were analyzed with a repeated measures ANOVA with Stimulus Intensity (two-pulse vs. five-pulse), Stimulation Side (left vs. right) and Session (rating-session 1 to 4) as within-subject factors. The differences between two-pulse and five-pulse electrical stimuli, stimulation side and time were further assessed with contrast analyses.

Responses faster than 100 ms were considered as anticipations and were omitted from the behavioral analyses. Outliers (RT > 3 SD above the individual mean) were also removed from the behavioral data. On average nine trials (2.2%) per participant were excluded from the analysis. RT and accuracy data were evaluated by using a repeated measures ANOVA with the factors Stimulation Side (left vs. right), Stimulus Intensity (two-pulse vs. five-pulse), Cue Validity (valid vs. invalid), and Hand Position (normal vs. crossed-hands).

The recorded EEG was analyzed using Brain Vision Analyzer (version 2.02.5859; Brain Products GmbH). First, a time window around the onset of each directional cue from –100 to 2000 ms was selected. The mean amplitude from –100 to 0 ms before cue onset served as a baseline. Trials with vertical and horizontal eye movements exceeding  $\pm 60$   $\mu$ V during the orienting phase were excluded. ICA (independent component analysis) ocular correction was applied to correct the EEG for remaining eye movement-related activity. An average of only 2% of the trials per participant was excluded from the following analyses.

#### 2.5.1. EEG analyses for the cue-stimulus interval

For analyses of the cue-stimulus interval a time window around the onset of each directional cue from –100 to 1000 ms was selected. Trials with artifacts were excluded with maximum/minimum allowed amplitudes of  $\pm 150$   $\mu$ V. ERLs were computed for the normal and crossed-hands conditions. We examined the electrode pairs C5/C6, FC5/FC6 and PO7/PO8 in twenty subsequent 40 ms time windows from 200 until 1000 ms after cue onset. The large number of statistical tests increases the chance of a type I error. To reduce this possibility, effects were considered significant only when two or more consecutive intervals showed an effect. The critical  $p$ -value can then be determined as  $\sqrt{0.05/((nr. \text{ time windows} - 1) * nr. \text{ electrodes})}$ , which here amounts to 0.0296. We decided to use a significance criterion of 0.02 (for comparable procedures, see Talsma et al., 2001; Van der Lubbe et al., 2014).

The LPS were computed for artifact-free trials in which attention was directed to the left or right side in the normal and crossed-hands conditions. We first extracted the power of the lower and upper alpha bands by performing a wavelet analysis on the raw EEG. A complex Morlet wavelet ( $c = 5$ ) was chosen with Gabor normalization. The following frequency bands were extracted: alpha-low ( $\alpha_1$ : 7.2–10.7 Hz), and alpha-up ( $\alpha_2$ : 9.4–14.0 Hz). Individual averages of these estimates were computed for both normal and crossed hands conditions per side of the relevant condition. Next, normalized lateralization indices ( $[\text{ipsilateral-contralateral}]/[\text{ipsilateral} + \text{contralateral}]$ ) were calculated for the different frequency bands, both for the left and right relevant side for symmetrical electrode pairs. By computing an average across the indices for both relevant sides, the LPS is derived (see Van der Lubbe and Utzerath, 2013). A positive deflection indicates larger ipsilateral than contralateral power, while a negative deflection would imply an opposite effect. We restricted the LPS analyses to the same electrode pairs as for the ERL analyses (C5/C6, FC5/FC6 and PO7/PO8), and examined the same twenty subsequent 40 ms time windows from 200 until 1000 ms after cue onset. Now, the critical  $p$ -value amounts to 0.0209 as two bands are involved. We decided to apply the same significance criterion (0.02) as for the ERLs.

2.5.2. ERP analyses for the processing of the intracutaneous electrical stimuli

A time window around each intracutaneous stimulus from -100 to 900 ms was selected. The mean amplitude from -100 to 0 ms before stimulus onset served as the baseline. Individual channels with artifacts were excluded with maximum/minimum allowed amplitudes of +/- 150 µV. Next, appropriate time windows and electrodes for analyses of the N1 and P3a components were selected based on inspection of the grand means. We analyzed the following components: N1: 165–185 ms on C5 and C6, and P3a: five 40 ms-time windows between 200 and 400 ms on Cz. Obtained averages (across trials without eye movements and EEG artifacts) per individual were subjected to repeated measures ANOVAs with the factors Stimulation Side (left vs. right), Stimulus Intensity (two-pulse vs. five-pulse), Cue Validity (valid vs. invalid), and Hand Position (normal vs. crossed-hands). For the analysis of the amplitude of the N1 component the factor Electrode (either ipsilateral vs. contralateral to the stimulated hand) was used instead of the factor Stimulus side. For the analysis of the amplitude of P3a component the factor Time (five 40 ms-time windows) was added. Greenhouse-Geisser ε correction was applied to the repeated measures ANOVA to correct for violations of the sphericity assumption whenever appropriate.

3. Results

3.1. Behavioral data

Analyses of the VAS scores (see Fig. 1) revealed that five-pulse electrical stimuli were judged as more painful than two-pulse stimuli (4.6 vs. 2.8;  $F(1,15) = 43.8, p < 0.001$ ). The scores also revealed that the intensity ratings attenuated over time ( $F(4,60) = 13.4, \epsilon = 0.49, p < 0.001$ ). Namely, lower stimulus intensity ratings were observed after the first block (rating session 2) as compared to the start of the experiment (rating session 1),  $F(1,15) = 10.6, p = 0.005$ . A significant decrease in stimulus intensity ratings was also observed between the fourth and the fifth rating session ( $F(1,15) = 9.8, p = 0.007$ ). No differences were observed in the stimulus intensity ratings between stimuli applied to either the left or to the right forearm ( $F(1,15) = 0.4, p = 0.518$ ).

The overall accuracy of the responses was 79.4% (SE: 2.1), with an accuracy of 79.8% (2.4) in normal trial blocks and of 78.9% (2.1) in crossed-hands blocks, which appeared to be quite comparable ( $F(1,15) = 0.1, p = 0.796$ ). No effect on response accuracy of Side of

Stimulation ( $F(1,15) = 0.2, p = 0.659$ ) and Cue Validity ( $F(1,15) = 0.3, p = 0.604$ ) was observed. In contrast, the accuracy of the responses to five-pulse stimuli was with 69.3% (3.0) significantly lower than with the two-pulse stimuli, which was 89.0% (2.1) ( $F(1,15) = 45.0, p < 0.001$ ).

RTs (see Fig. 1) were faster for validly cued stimuli (939 ms) than for invalidly cued stimuli (1002 ms), ( $F(1,15) = 7.7, p = 0.014$ ). No difference in RT was observed between normal (951 ms) and crossed hands blocks (989 ms;  $F(1,15) = 1.9, p = 0.193$ ). Furthermore, stimulus intensity had no effect on RT ( $F(1,15) = 0.5, p = 0.488$ ). Additionally, no effect of Side of Stimulation was observed ( $F(1,15) = 1.9, p = 0.192$ ). Finally, no interaction was observed between the factors Hand Position and Cue Validity ( $F(1,15) = 0.0, p = 0.940$ ). In addition, no significant interactions were observed between any of the other factors ( $F < 4.0, p > 0.065$ ).

3.2. EEG data

3.2.1. Attentional orienting

3.2.1.1. ERL data. Analyses on the ERLs (see Fig. 2) revealed the presence of an EDAN over occipital sites (PO7/PO8) from 200 to 360 ms (see Table 1). An ADAN was observed over lateral fronto-central sites (FC5/FC6) from 240 to 960 ms (-2.2 to -5.4), which extended over lateral central sites (C5/C6) from 320 to 520 ms. Visual inspection of the grand average waveforms shows a positivity around 560 to 640 ms over occipital sites, which represents an LDAP. However, this positive lateralization was only significant for one time window (560 to 600 ms;  $F(1,15) = 6.8, p = 0.020$ ) and therefore did not meet the two consecutive time windows criterion. Furthermore, no differences in ERLs were observed between normal and crossed-hands blocks (there were no consecutive time windows in which the critical value was of 0.02 was crossed).

3.2.1.2. LPS data. LPS data are displayed in Fig. 3 and results of statistical analyses are displayed in Table 2. Increased ipsilateral occipital power (PO7/PO8) was observed for the lower  $\alpha_1$  band from 360 to 600 ms ( $F > 6.9, p < 0.0019$ ) and for the upper  $\alpha_2$  band from 360 to 680 ms ( $F > 6.5, p < 0.02$ ). An increase in ipsilateral power over lateral central sites (C5/C6) was observed for the lower  $\alpha_1$  band from 240 to 600 ms ( $F > 7.4, p < 0.016$ ) and for the upper  $\alpha_2$  band from 360 to 560 ms ( $F > 8.2, p < 0.012$ ). Finally, increased ipsilateral power over lateral central sites (C5/C6) was observed for the lower  $\alpha_1$  band from 920 to 1000 ms ( $F > 7.9, p < 0.013$ ).

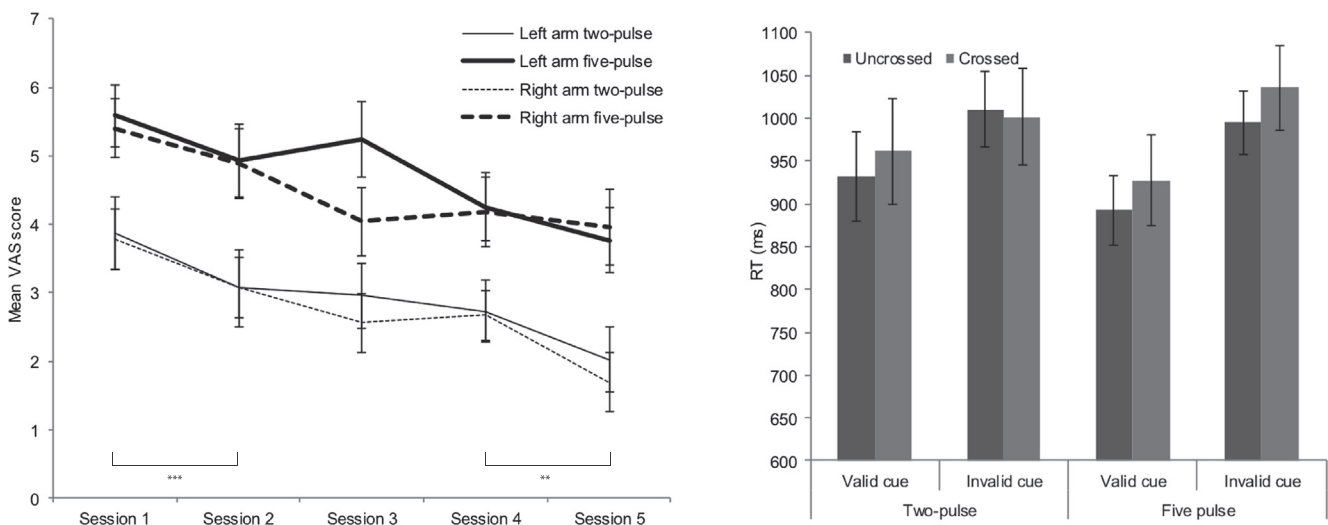


Fig. 1. In the left panel, the mean stimulus intensity ratings for two-pulse and five-pulse stimuli delivered at the left and right forearm obtained with a visual analog scale (VAS) in the first (before start of block 1), the second, the third, the fourth, and the fifth session are displayed. Mean RTs for validly and invalidly cued two-pulse and five-pulse stimuli in the normal and crossed-hands blocks are displayed in the right panel. In both panels, error bars represent standard errors of the mean (\* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.005$ ).

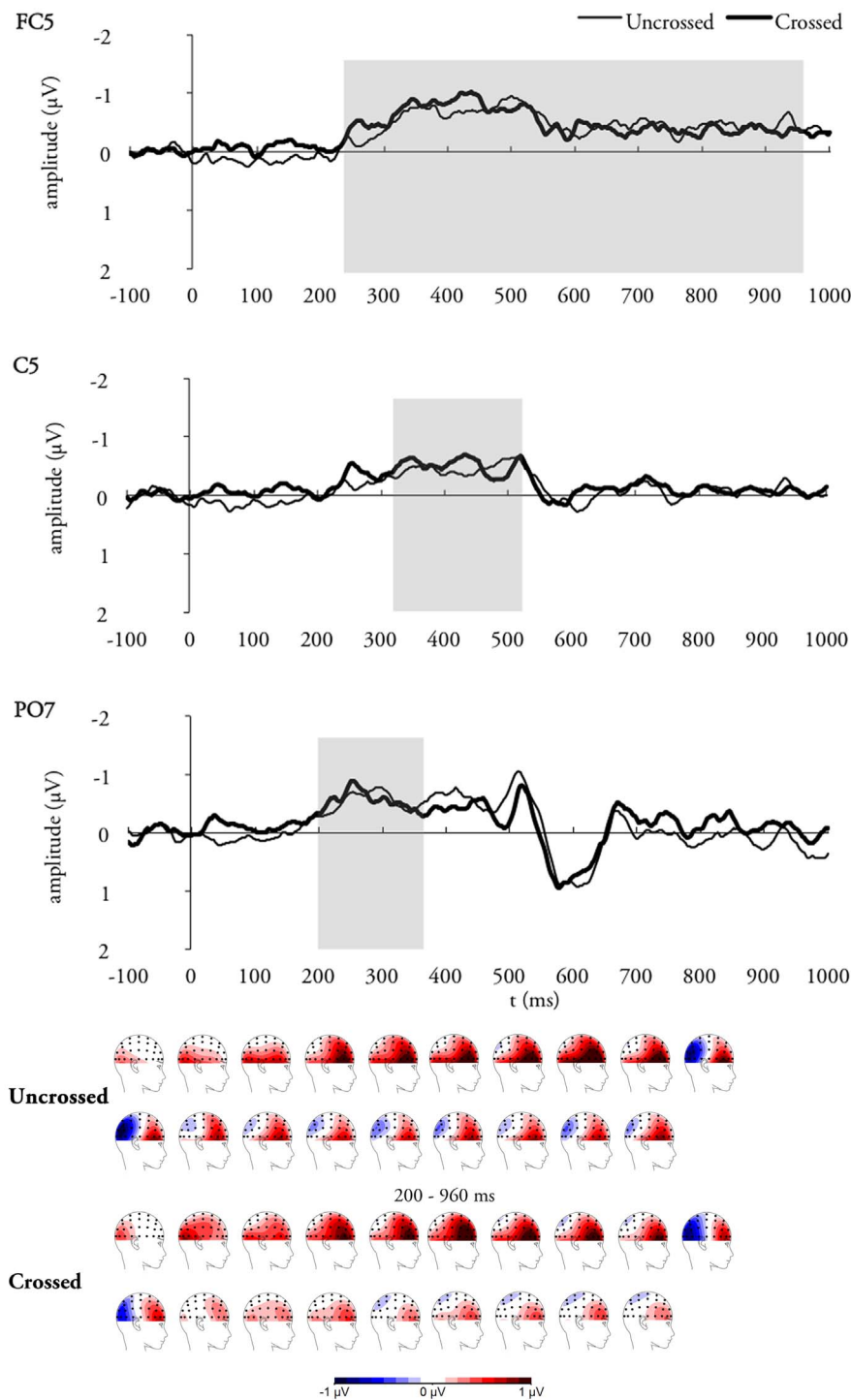


Fig. 2. Grand average event related lateralizations (ERLs) observed during the cue-stimulus interval at lateral fronto-central, central and occipital sites are displayed. Significant deviations from zero are indicated with light grey boxes. Topographical maps (right hemisphere) displaying the ipsi-contralateral difference map of the ERLs in 40 ms windows for relevant time windows are shown separately for normal and crossed-hands blocks. In the left hemisphere, the contra-ipsilateral difference map is displayed, whereas the inverted ipsi-contralateral difference map is presented in the right hemisphere.

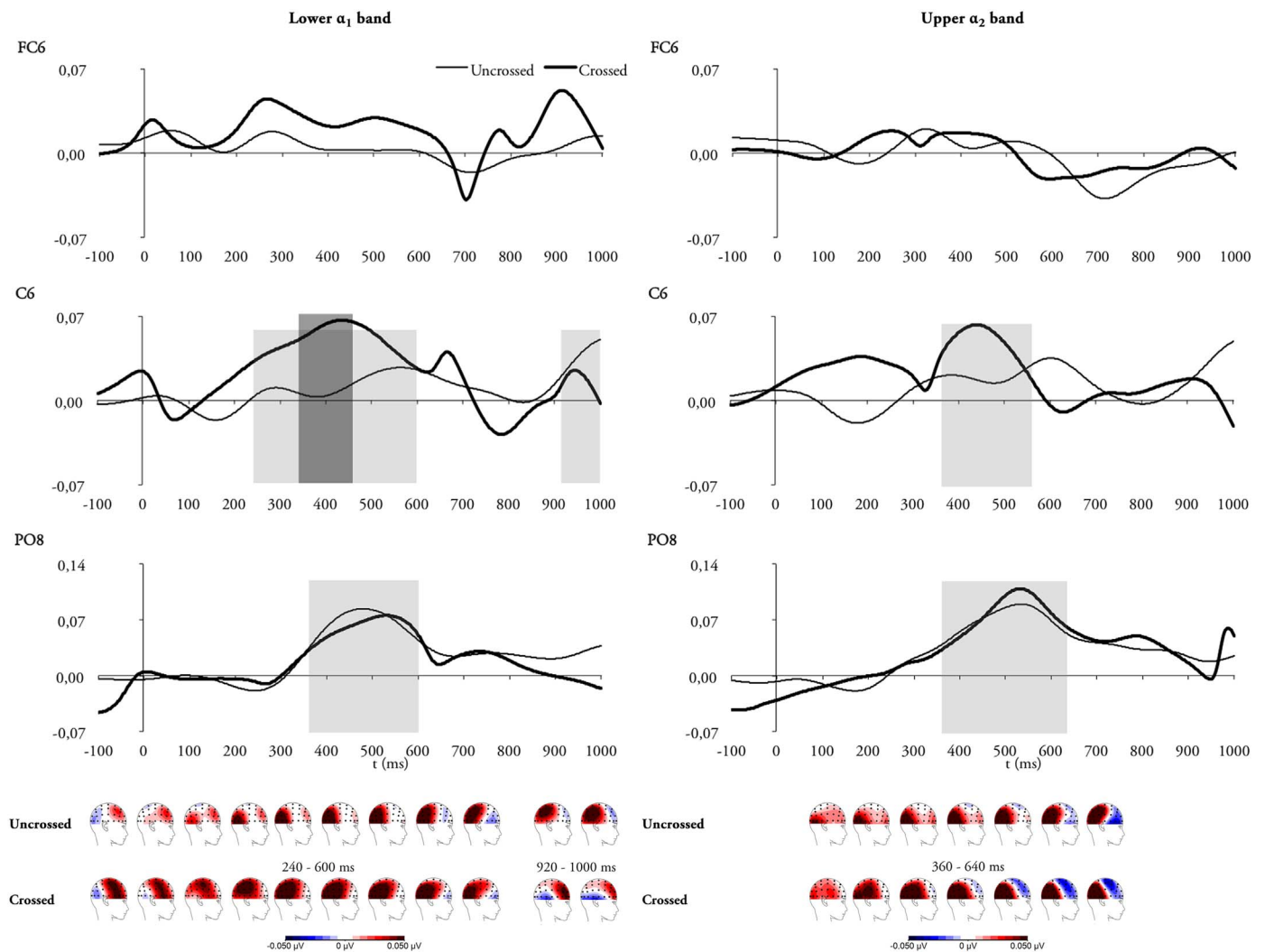
A difference in alpha activity between normal and crossed-hands blocks was observed from 360 to 400 ms on the lower  $\alpha_1$  band over lateral central sites (C5/C6). A larger ipsilateral increase in alpha

activity was observed in crossed-hands blocks than in normal hand position blocks ( $F > 9.5, p < 0.008$ ).

Table 1

Summary of the overall effects observed on the ERLs. Effects are described in terms of contra-ipsilateral differences, which in the displayed topographies are projected on the left hemisphere. EDAN = early directing attention negativity. ADAN = anterior directing attention negativity. LDAP = late directing attention positivity.

Window (ms)	Maxima	Deflection	$F(1,15)$	$p$	ERL component
200–360	PO7/PO8	Negative	7.8–20.8	0.001–0.014	EDAN
240–960	FC5/FC6	Negative	6.6–47.7	0.001–0.016	ADAN
320–520	C5/C6	Negative	10.6–28.8	0.001–0.005	



**Fig. 3.** The lateralized power spectra for the lower  $\alpha_1$  band (left) and upper  $\alpha_2$  band (right). Positive values mean increased ipsilateral relative to contralateral power. Light grey boxes indicate a significant deviation from zero. Dark grey boxes indicate significant differences between the normal and the crossed-hands blocks. The topographical maps (right hemisphere reflecting the ipsi-contralateral difference) of the lower  $\alpha_1$  band and upper  $\alpha_2$  band are also displayed for relevant 40 ms time windows (top: normal, lower: crossed-hands). Positive values for the right hemisphere reflect increased ipsilateral as compared to contralateral power.

**Table 2**

A summary of the overall results for the LPS analyses. The table shows the time windows and electrode pairs where the power in the two alpha bands significantly deviated from zero. All effects are described in terms of ipsi-contralateral differences.

Power					
Window (ms)	Band	Maxima	Deflection	$F(1,15)$	$p$
240–600	$\alpha_1$	C5/C6	Increase	7.4–29.0	0.001–0.016
360–560	$\alpha_2$	C5/C6	Increase	8.2–12.9	0.003–0.012
360–600	$\alpha_1$	PO7/PO8	Increase	6.9–17.6	0.001–0.019
360–640	$\alpha_2$	PO7/PO8	Increase	10.3–19.4	0.001–0.006
920–1000	$\alpha_1$	C5/C6	Increase	7.9–8.5	0.011–0.013

### 3.2.2. ERPs of the intracutaneous electrical stimuli

Inspection of the topographical maps (see Fig. 4) shows that the N1 component was maximal at the C5 or C6 electrode contralateral to the stimulated forearm. The P3a component was maximal at the vertex (Cz; see Fig. 5).

**3.2.2.1. The N1 component.** The N1 component (see Fig. 4) was larger for five-pulse than for two-pulse electrical stimuli ( $-1.7$  vs.  $-1.4$   $\mu\text{V}$ ;  $F(1,15) = 8.7$ ,  $p = 0.010$ ) and also larger at contralateral than at

ipsilateral electrodes ( $-2.5$  vs.  $-0.7$   $\mu\text{V}$ ;  $F(1,15) = 29.6$ ,  $p < 0.001$ ). No effects were observed of Cue Validity ( $F(1,15) = 0.1$ ,  $p = 0.738$ ) and Hand Position ( $F(1,15) = 0.5$ ,  $p = 0.509$ ). In addition, no interactions were observed ( $F(1,15) < 4.3$ ,  $p > 0.055$ ).

**3.2.2.2. The P3a component.** The P3a component (see Fig. 5) was significantly larger for five-pulse than for two-pulse stimuli ( $3.7$  vs.  $2.4$   $\mu\text{V}$ ;  $F(1,15) = 23.2$ ,  $p < 0.001$ ). Furthermore, the P3a component ( $F(1,15) = 7.5$ ,  $p = 0.015$ ) was larger after invalid than after valid cues ( $3.4$  vs.  $2.7$   $\mu\text{V}$ ). No overall differences were observed between the normal ( $3.1$   $\mu\text{V}$ ) and the crossed-hands blocks ( $3.0$   $\mu\text{V}$ ;  $F(1,15) = 0.3$ ,  $p = 0.585$ ). Furthermore, no differences were observed between the two sides of stimulation. The amplitude of the P3a component increased from  $2.9$   $\mu\text{V}$  in the first time window (200 to 240 ms) to  $3.6$   $\mu\text{V}$  in the third time window (280 to 320 ms), and then decreased to  $2.4$   $\mu\text{V}$  in the time window from 360 to 400 ms (Time;  $F(4,60) = 3.4$ ,  $\epsilon = 0.59$ ,  $p = 0.037$ ). An interaction was observed between the factors Time and Cue Validity ( $F(4,60) = 4.3$ ,  $\epsilon = 0.42$ ,  $p = 0.029$ ), showing a larger decrease in amplitude of the P3a component in response to validly cued stimuli in from 320 to 360 ms and from 360 to 400 ms. Furthermore, an interaction between Time and Hand Position was observed ( $F(4,60) = 2.9$ ,  $\epsilon = 0.72$ ,  $p = 0.048$ ).

Separate analyses for the normal and the crossed-hands blocks

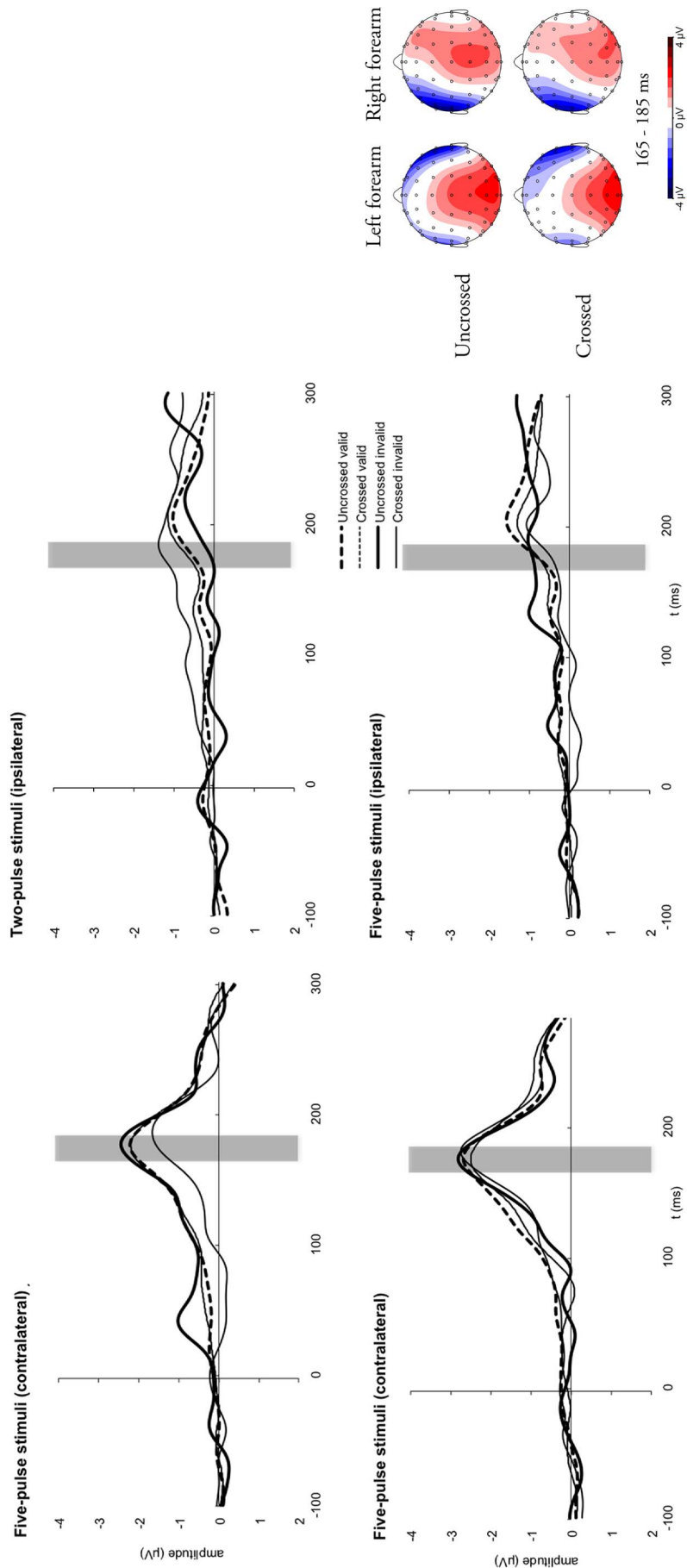


Fig. 4. Grand average ERPs showing the N1 component (contralateral and ipsilateral) in response to the presented intracutaneous stimuli. The grey time window highlights the N1 component and the analyzed time window. Topographical maps of the N1 component in response to validly cued high intensity stimuli in the time window 165–185 ms after stimulus onset (top: normal, lower: crossed-hands; left: stimuli presented to the left forearm, right: stimuli presented to the right forearm).



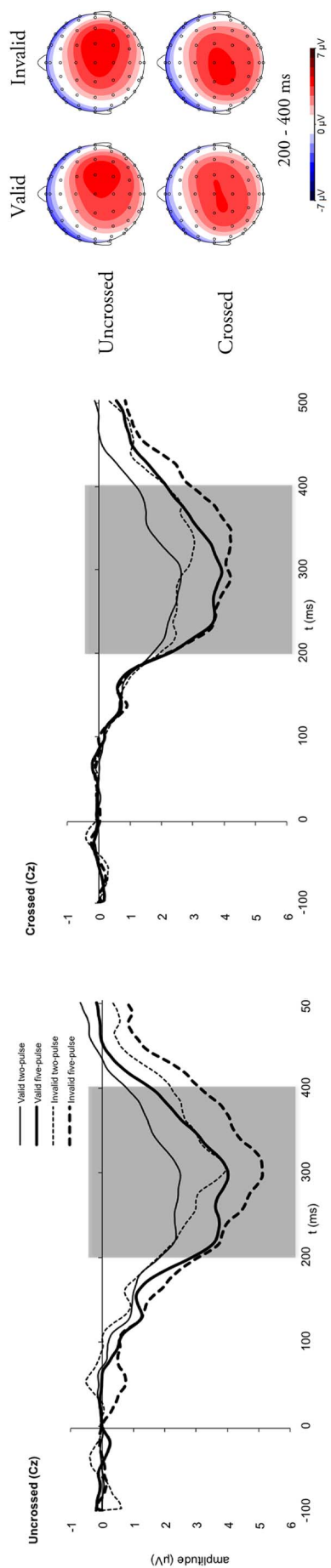


Fig. 5. ERPs determined for the Cz electrode in response to the presented stimuli. The grey time window highlights the P3a component and the analyzed time windows. Topographical maps of the P3a component in response to high intensity stimuli are presented on the left side for the 200–400 ms time window after stimulus onset (top: normal, lower: crossed-hands; left: validly cued, right: invalidly cued).

revealed that an effect of time was only observed in the normal blocks ( $F(4,60) = 4.7, \eta^2 = 0.57, p = 0.013$ ). The amplitude of the P3a component increased from  $3.0 \mu\text{V}$  in the 200 to 240 ms time window, to  $3.8 \mu\text{V}$  in time window from 280 to 320 ms, while it decreased to  $2.1 \mu\text{V}$  in the time window from 360 to 400 ms. No effect of Time was observed in the crossed-hands blocks ( $F(4,60) = 1.9, \eta^2 = 0.59, p = 0.151$ ).

Separate analyses for the normal and the crossed-hands blocks also revealed a difference in effects on the factor Cue Validity as a function of Hand Position. Namely, the P3a component was larger on invalidly cued than on validly cued stimuli in blocks with a normal hand position ( $3.6$  versus  $2.6 \mu\text{V}$ ;  $F(1,15) = 8.8, p = 0.009$ ), while no validity effect was observed in crossed-hands blocks ( $2.7$  versus  $3.2 \mu\text{V}$ ;  $F(1,15) = 2.8, p = 0.112$ ).

#### 4. Discussion

The aim of the present study was to examine whether orienting attention while awaiting intracutaneous electrical stimuli (i.e., endogenous orienting) predominantly occurs within an internal somatotopic reference frame or within an external body-centered reference frame. Stimuli that activate the nociceptive system are likely to automatically direct attention (i.e., exogenous orienting) to an affected body part, which will facilitate fast actions to cope with a potential life-threatening situation. These actions generally concern changes of body parts or the whole body in external space so one might favor the idea that the external reference frame will also be involved while anticipating intracutaneous stimuli. Alternatively, if attention serves an important role as a pain modulator then an influence within an internal reference frame may make more sense. To enable an answer to the question what reference frame is involved we used blocks in which participants had their hands in a normal or a crossed-hands position while they were anticipating intracutaneous electrical stimuli on their left or right forearms. EEG was measured to examine the orienting phase and the processing of the stimuli.

An essential aspect to assess whether our participants indeed focused their attention on the forearm on the relevant side is to examine whether responses were faster for cued targets than for uncued targets, both in blocks with a normal hand position and in the crossed-hands blocks. Our RT results confirmed the presence of a cue validity effect independent from the type of block, which suggests that attention was properly directed in both blocks. This, however, does not imply that attentional orienting in both blocks was the same.

Two methods of analyzing the EEG were used which may shed a light on the direction of attention while awaiting the intracutaneous electrical stimuli. The ERL method extracts the electrophysiological activity that is time-locked and phase-locked to a cue that signals the to-be-attended side, while the LPS method also allows to determine activity that is time-locked but not necessarily phase-locked by determining lateralized power in specific frequency bands. Here we decided to focus on the lower and higher alpha bands as these bands have been shown to be modulated both by attentional manipulations and manipulations involving hand-related activity (e.g., see Anderson and Ding, 2011; Klimesch et al., 2007; Pfurtscheller et al., 1997).<sup>2</sup>

ERL results revealed the commonly observed EDAN and ADAN components, while the LDAP seemed present but did not satisfy our significance criterion. Importantly, no influence of Hand Position was observed which confirms the view that attentional orienting occurred within an external reference frame. The LPS results revealed increased ipsilateral occipital alpha power (both in the lower and higher alpha bands) and additionally increased ipsilateral central alpha (or mu)

<sup>2</sup> Some recent studies (e.g., see Tiemann et al., 2010) revealed that gamma oscillations are as well sensitive to attentional effects of pain. We decided not to focus on these higher frequencies as earlier analyses on data of other experiments in our lab suggest that our experimental setup and recording conditions were not yet optimal for examining gamma oscillations due to high noise levels around 50 Hz.

power. Interestingly, this increased ipsilateral alpha power above somatosensory areas was also present shortly before the onset of the nociceptive stimuli. No support was found for a reversal in the crossed-hands blocks, there was even larger ipsilateral central alpha power in the crossed-hands blocks halfway the orienting phase. Together these EEG results indicate that the direction of attention during the orienting phase occurred within an external reference frame. This effect was not limited to visual brain areas as we also observed modulation on electrodes above somatosensory areas. The increased ipsilateral power in the alpha bands implies that power was lower above contralateral sites. The common interpretation of this effect is that it reflects reduced inhibition of contralateral brain areas and/or increased inhibition of ipsilateral brain areas (e.g., see Klimesch, 1997). An earlier study with tactile stimuli by Gherrri and Forster (2012) reported an LDAP over posterior sites contralateral to the cue side of space that was unaffected by hand position. Furthermore, an ADAN was observed that was also not affected by the position of the hands. However, later in the orienting phase an enhanced negativity was observed over central sites, which was reversed in polarity in the crossed hands position. Thus, this activity appeared to depend on an internal reference frame. No such effect was observed in our study. Thus, it may be proposed that orienting while anticipating tactile stimuli is slightly different. Nevertheless subtle differences in task instructions may play a role (see below), therefore, it seems too early to conclude that there are differences depending on the type of anticipated stimuli.

ERPs evoked by the intracutaneous electrical stimuli also provide information about the involved reference frame, as absence of an effect of hand position on the N1 and P3a component would suggest that at this stage orienting occurs within an internal reference frame. The N1 component was larger on contralateral than on ipsilateral electrodes, and also larger for more intense (five-pulse) than less intense (two-pulse) stimuli. No effects of attentional orienting and hand position were observed. Thus, the common N1 enhancement for attended stimuli (e.g., see Blom et al., 2012; Van der Lubbe et al., 2012b, 2017) was not observed in the current study. A possible explanation is that some slight differences in the employed tasks may have played a role. In the current experiment all electrical stimuli were relevant as responses were required to both validly and invalidly cued stimuli, while in the abovementioned studies unattended stimuli required no response (i.e., NoGo trials). Possibly, this increased relevance of unattended stimuli may have cancelled the commonly observed modulation within somatosensory areas. Thus, it seems that endogenous orienting had no influence at this processing level.

Overall, results for the P3a component replicate the earlier observation of increased amplitudes for invalidly cued relative to validly cued trials (see Van der Lubbe et al., 2012b, 2017). In those studies we reasoned that this effect reflects a “call for attention” (see Polich, 2007) as alternative explanations like response inhibition on NoGo trials seemed improbable as there was no strong emphasis on fast responding in these studies and as the majority of trials did not require a response. In the current paradigm, response inhibition seems even more unlikely as responses were required on all trials. Therefore, we again favor an interpretation of this effect as a “call for attention”. This interpretation can also account for the enlarged P3 component after more intense stimuli. Importantly, we observed an interaction involving the factor Hand Position, therefore, separate analyses were carried out for the normal and the crossed-hands blocks. In the blocks with a normal hands position we observed the increased P3a component for invalidly cued trials. In the crossed-hands blocks, this effect was not significant and even tended to be inverted. This observation suggests that there was no call for attention by the invalidly cued stimuli in this block, which may be ascribed to decreased efficiency in attentional selection due to conflicting reference frames (see Eimer et al., 2001).

Together, our ERL, LPS and ERP findings point to the conclusion that attentional orienting while anticipating intracutaneous electrical nociceptive stimuli primarily occurred within an external body-based

reference frame. Nevertheless, we think that some procedural aspects in our study may have prevented us from the possibility of finding support for the involvement of an internal reference frame, therefore, we think this is not the definite answer. Most important seems the precise instruction, as we simply asked our participants to attend to the side indicated by the relevant side of the cue. We did not explicitly ask our participants to direct their attention to the cued hand. Furthermore, the use of directional visual cues may have introduced a bias to an external visually-based reference frame. A follow-up experiment with auditory cues telling “left hand” or “right hand” might very well reveal different results in normal and crossed-hands block. As indicated in our introduction, several reference frames can be distinguished, as reference frames may have retinal, head-centered, body-centered, hand-centered, and somatotopic reference points. Our external reference frame could actually refer to different reference points as the retina, the head, the body, and the feet were all aligned. Interestingly, the fact that results do not simply depend on the relevant hand but on the position of the relevant hand indicates that here endogenous orienting while anticipating intracutaneous stimuli has more to do with action relevance than with modulating activity in somatosensory brain areas.

Although we argued in our introduction that the stimulation technique that we employed preferentially activates nociceptive A $\delta$  fibers, we used stimulus intensities that on the basis of the results of Mouraux et al. (2010) may very well activate A $\beta$  fibers. However, our sensory thresholds were also substantially higher than in their study (see footnote 1), which indicates that it may be difficult to directly compare employed currents from different studies. One argument that favors the interpretation that our ERP effects primarily reflect nociceptive processing is a comparison with results of a pilot study in our lab with nearly the same setup in which we used transcutaneous stimuli. This comparison revealed that the N1 component in the current study was delayed (176 vs. 162 ms),<sup>3</sup> which seems in line with slower processing along nociceptive fibers. One might argue that this argument is not fully convincing as different participants took part in these studies. Therefore, probably the best idea to demonstrate that employed intracutaneous electrical stimuli selectively activate nociceptive fibers is to demonstrate that ERPs strongly reduce in amplitude when capsaicin is applied (see Mouraux et al., 2010) as a direct comparison on the basis of employed current amplitudes may not be a conclusive argument.

An interesting observation that is not related to the involvement of different reference frames is the decrease of sensation ratings over time. This is likely the result of the commonly observed habituation to the presented painful stimuli during an experiment (see also Blom et al., 2012). A consequence of this habituation may be that the contrast between high intensity and low intensity stimuli decreases during the experiment. As a result, participants may have adopted a more conservative strategy in which they classified the high intensity five-pulse stimuli as low intensity two-pulse stimuli. This may account for the relatively high proportion of errors in our study.

In conclusion, our EEG results favor the view that the orienting of attention while anticipating intracutaneous electrical stimuli primarily occurs with an external reference frame. Future studies with nonvisual cues, and manipulations that dissociate reference frames related to the retina, the head, or the body may reveal whether attention can also operate within different reference frames.

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<sup>3</sup> The N1 component peaked later in our experiment with intracutaneous electrical stimulation ( $t(30) = -5.2, p < 0.001; M = 176$  ms,  $SE = 1.8$ ) than in an earlier pilot study with transcutaneous stimulation ( $M = 162$  ms,  $SE = 2.0$ ).

authors declare no conflict of interest.

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