Defensive peripersonal space: the blink reflex evoked by hand stimulation is increased when the hand is near the face

C. F. Sambo,¹ M. Liang,¹ G. Cruccu,² and G. D. Iannetti¹
¹Department of Neuroscience, Physiology and Pharmacology, University College London, London, United Kingdom; and ²Department of Neurology and Psychiatry, La Sapienza University, Rome, Italy

Submitted 5 August 2011; accepted in final form 12 November 2011

Reflexes are involuntary and stereotyped responses to external stimuli, usually mediated by fast, subcortical pathways. Despite their relatively simple neural circuits, in a Sherringtonian sense reflex responses may be elaborated into flexible, adaptive behavior, by reacting to potentially aversive stimuli to avoid impending danger (Sherrington 1906). More sophisticated and nonstereotyped defensive behaviors are mediated by cortical mechanisms, occurring in associative areas such as the polysensory zone (PZ) in the precentral gyrus and the ventral intraparietal (VIP) area (Graziano and Cooke 2006). These cortical areas are thought to encode the peripersonal space, i.e., the region of space surrounding the body (Macaluso and Maravita 2010). From an evolutionary point of view, such a representation has been interpreted as being due to the shorter conduction distance and, consequently, the more synchronized afferent volleys generated by stimuli applied to the upper limb (Alvarez-Blanco et al. 2009). This has been interpreted as well due to the shorter conduction distance and, consequently, the more synchronized afferent volleys generated by stimuli applied to the upper limb (Alvarez-Blanco et al. 2009). However, an additional explanation is possible: that the greater proximity of the upper limb to the face is responsible for the larger BR elicited by upper limb stimulation. Indeed, one may expect that the perceived threat of stimuli increases when the stimulated body part is closer to the face, thus resulting in a larger BR.

Here we tested this hypothesis with a series of experiments aiming to answer three main questions. First (experiments 1 and 3), we explored whether the magnitude of the BR elicited by electrical stimulation of the median nerve at the wrist [hand blink reflex (HBR)] is increased when the stimulated hand enters the peripersonal space surrounding the face. If the HBR is affected by hand position, this would suggest that the brain stem circuits mediating the HBR undergo top-down modulation from higher order cortical areas responsible for encoding the peripersonal space of the face, as such as贵宾 and PZ.
Notably, these areas are also thought to compute the location of somatosensory stimuli with respect to the position of the body parts in external space (Azanon et al. 2010; Lloyd et al. 2003; Medina and Coslett 2010). Second (experiment 2), because vision affects somatosensory processing and perception of limb position (Longo et al. 2008; Ro et al. 2004; Sambo et al. 2009; Taylor-Clarke et al. 2002; van Beers et al. 1999), we tested whether vision of the stimulated hand modulates the possible effect of hand position on the HBR. Third (experiments 4 and 5), we investigated at which level of the somatosensory pathway the top-down modulation of the HBR takes place. If this modulation consists in a facilitation at the level of the motoneurons innervating the orbicularis oculi muscle, then hand position would modulate not only the magnitude of the HBR, but also that of the BR elicited by the electrical stimulation of the supraorbital nerve (experiment 4). On the other hand, if the top-down modulation takes place in the cuneate nucleus, at the level of the first synapse of the lemniscal pathway (i.e., before top-down modulation takes place in the cuneate nucleus, at the but also that of the BR elicited by the electrical stimulation of). We placed on the median nerve at the wrist (HBR). This was achieved by increasing the stimulus intensity until a clear HBR was observed in three consecutive trials, or the participant refused a further increase of stimulus intensity (Valls-Solé et al. 1997). Only participants showing a reproducible HBR (i.e., “responders”), N = 12; five women, mean age ± SD: 29.2 ± 5.7 yr underwent further testing. In these participants, we performed five separate experiments.

Experiment 1. To investigate the effect of “hand position” on the HBR, in the 12 responders, we recorded HBR responses in two experimental conditions. In the “far” condition, participants were balanced across participants. In each block, 10 stimuli were delivered in the far and 10 in the near condition, in alternating trials. Participants changed the position of their arm after each trial. One-half of the participants started the block with a stimulus in the far condition, and one-half with a stimulus in the near condition. During each block, participants were instructed to keep their gaze on a small fixation cross (1.5 cm²) placed at ~30 cm and 45° below eye level. White noise was played throughout the experiment to mask any sound possibly arising from the stimulation procedure.

Experiment 2. To investigate the contribution of the vision of the stimulated hand to the effect observed in experiment 1, in eight responders we recorded the HBR in the far and near experimental conditions, while they kept their eyes closed throughout each of the two recording blocks. The experimental procedures used were otherwise similar to experiment 1.

Experiment 3. To control the effect of hand position on the HBR was affected by the different proprioceptive input from the arm in the far and near conditions, in six responders we recorded the HBR while the position of both the hand and the arm was kept constant, and the proximity of the stimulated hand to the face was manipulated by rotating the head. Thus, the participants’ forearm was kept flexed in the same near position all the time, and their head was either kept straight in anatomical position (“near-front” condition) or rotated sideways by 90° (“near-side” condition) (see Fig. 5). Similar to experiment 1, a total of 40 electrical stimuli were delivered to the median nerve, 20 stimuli to the left wrist and 20 stimuli to the right wrist, in separate blocks. The order of blocks was balanced across
Hand blink reflex - stimulation and recording setup

Stimulation: median nerve
(200 μs, 20-80 mA, ~30s ISI)

Recording: orbicularis oculi
(20 superimposed trials)

HAND FAR
Contralateral (n=20)
Ipsilateral (n=20)

HAND NEAR
Contralateral (n=20)
Ipsilateral (n=20)
participants. In each block, 10 stimuli were delivered in the near-front and 10 in the near-side condition, in alternating trials.

**Experiment 4.** To further control whether the effect of hand position on the HBR reflected a modulation of the excitability of the orbicularis oculi muscle due to the change of upper-limb position, in six responders we recorded the BR elicited by the electrical stimulation of the supraorbital nerve, in the far and near experimental conditions, as in experiments 1 and 2. In this experiment, electrical stimuli were delivered, with equal probability, either to the right supraorbital nerve, or to the median nerve of the right hand (i.e., the hand undergoing the postural manipulation). Participants did not know in advance if the median or the supraorbital nerve would be stimulated: this was done to ensure that the position of the hand with respect to the face was as relevant as in experiments 1–3 and 5, where stimuli were always delivered to the median nerve of the hand undergoing the postural manipulation. A total of 40 stimuli were delivered, 20 to the supraorbital nerve and 20 to the median nerve and, for each site, 10 in the far and 10 in the near condition, in alternating trials. The stimuli were delivered in pseudorandom order, with no more than three consecutive stimuli delivered to the same body site.

**Experiment 5.** To rule out the possibility that the effect of hand position on the HBR resulted from a reduced presynaptic inhibition on the primary Aδ afferents, in six responders we recorded the N20 wave of the SEPs elicited by the electrical stimulation of the median nerve at the wrist, in the same two experimental conditions (far and near). In this experiment, 600 electrical stimuli were delivered to the right wrist, 300 in the far condition and 300 in the near condition, in alternating blocks of 100 stimuli each.

**Data Analysis and Statistics**

Both EMG and EEG signals were analyzed using Letswave (http://amouraux.webnode.com) (Mouraux and Iannetti 2008). EMG signals from each participant were high-pass filtered (55 Hz), full-wave rectified, and averaged separately for the far and near conditions (or near-front and near-side conditions in experiment 3) at the ipsilateral and contralateral recording sides. In each participant, we measured the onset latency, duration, and area of the HBR for each experimental condition and recording side. In experiments 1 and 2, for each of these measures, we performed a two-way, repeated-measures ANOVA, with hand position (two levels: far and near) and “recording side” (two levels: “ipsilateral” and “contralateral”) as experimental factors. In experiment 3, data were averaged across ipsilateral and contralateral recording sides.

Furthermore, to investigate the time course of the possible effects of hand position and recording side in experiment 1, we performed the same repeated-measures ANOVA, but using each time point of the averaged reflex response, as implemented in Letswave (Mouraux and Iannetti 2008). In those participants who took part in experiment 2, we also performed a point-by-point, two-way repeated-measures ANOVA, with hand position (two levels: far and near) and “vision” (two levels: “eyes open” and “eyes closed”) as experimental factors. Each point-by-point ANOVA yields three waveforms expressing the significance of the effect of each of the two factors across time and their interaction. In experiment 3, we performed a similar point-by-point analysis, consisting in a paired r-test with “head position” (two levels: near-front and near-side) as experimental factor. In all analyses, a consecutivity threshold of 10 ms was chosen to account for multiple comparisons.

EEG signals from each participant were averaged separately for the far and near conditions. In each participant, we measured the peak amplitude and latency of the N20 wave of the SEPs for each condition.

In all statistical analyses, the significance level (α) was set at 0.05.

**RESULTS**

We observed a clear and reproducible HBR in 12 out of 20 participants (60%), using a stimulus intensity ranging between 4 and 53 times the individual perceptive threshold. These 12 participants were considered as responders and were included in further analyses.

**Experiment 1**

Figures 1 (left) and 2 show the HBR waveforms recorded in one representative participant (as superimposed single trials) and in all 12 participants (as single-subject averages), respectively, in the far and near conditions at the contralateral and ipsilateral recording sides. Importantly, as shown in the single-trial response plots (Fig. 1, right), although there was some degree of variability in the responses, which is expected for a reflex mediated by a polysynaptic circuit in the reticular formation (Cruccu et al. 2006), the magnitude of the HBR was not reduced throughout the recording. This indicates that, when using a constant intertrial interval of 30 s, the HBR does not habituate over time.

Effect of hand position and recording side on onset latency and duration of the HBR. The onset latency of the HBR was shorter when the stimulated hand was inside the area of peripersonal space surrounding the face (near: 45.5 ± 7.5 ms) than when it was outside (far: 50.3 ± 7 ms), and when the stimulated hand was ipsilateral (46.8 ± 7.2 ms) than contralateral (49.7 ± 7.3 ms) to the recording side. This was reflected in a significant main effect of hand position [F(1,11) = 19.07, P = 0.001, η² = 0.64] and recording side [F(1,11) = 29.98, P = 0.001, η² = 0.73] on the HBR onset latency (two-way, repeated-measures ANOVA). The interaction between the two factors was not significant (P = 0.65).

Likewise, the duration of the HBR was longer in the near (50.2 ± 9.3 ms) than in the far condition (40.1 ± 12.5 ms), and at the ipsilateral (47.6 ± 10.8 ms) than at the contralateral (42.7 ± 11 ms) recording side. There was a significant main effect of hand position [F(1,11) = 14.55, P = 0.003, η² = 0.57] and recording side [F(1,11) = 9.61, P = 0.01, η² = 0.47] on the HBR duration (two-way, repeated-measures ANOVA). The interaction between the two factors was not significant (P = 0.19).

Fig. 1. **Top:** schematic representation of the stimulation and recording setup (experiments 1–3). The hand blink reflex (HBR) was elicited by electrical stimulation of the median nerve at the wrist and recorded from the orbicularis oculi (OO) muscle. ISI, interstimulus interval. **Middle and bottom:** experiment 1. **Left:** rectified and superimposed single-trial HBR waveforms from one representative participant. x-axis, time (ms); y-axis, EMG activity (mV). **Middle:** “far” condition. The HBR was elicited while participants were sitting with their forearm at ~120° with respect to the arm, and with the hand close to the ipsilateral knee. **Bottom:** “near” condition. The HBR was elicited while participants were sitting with their forearm at ~75° with respect to the arm, and their hand close by ~4 cm to the ipsilateral side of their face. Note that the HBR has a significantly greater magnitude in the “near” than in the “far” condition, and at the “ipsilateral” than at the “contralateral” recording side. Right: to emphasize the lack of response habituation to repetitive stimulation, one bidimensional plot of single-trial responses is shown for each condition and recording side. Horizontal lines in the plot represent single-trial EMG responses, with signal amplitude color-coded at each time point. Responses are sorted vertically in order of occurrence, from bottom (first trial) to top (last trial). The waveform below each plot is the average of all responses.
Effect of hand position and recording side on HBR magnitude. The magnitude of the HBR, as measured by the area under the curve (AUC), was significantly larger when the stimulated hand was inside the peripersonal space of the face [near: 128 ± 50, far: 71 ± 37 AUC arbitrary units; +99.3 ± 60.2%; main effect of hand position, \( F_{(1,11)} = 75.70, P < 0.001, \eta^2 = 0.87 \)], and when the stimulated hand was ipsilateral to the recording side [ipsilateral: 111 ± 46, contralateral: 88 ± 40 AUC arbitrary units; +28.6 ± 19.2%; main effect of recording side, \( F_{(1,11)} = 39.42, P < 0.001, \eta^2 = 0.78 \)].

Fig. 2. Experiment 1. Top: rectified and superimposed average of each participant (\( N = 12 \)) for the far and near conditions, at the contralateral and ipsilateral recording sides. Each participant is represented by a different color. Bottom: group-average HBR waveforms in the far and near conditions, at the contralateral and ipsilateral recording sides. x-axis, time (ms); y-axis, EMG activity (mV).
interaction between the two factors was not significant \((P = 0.18)\).

Effect of hand position and recording side on HBR magnitude across time. To investigate the time course of the effects of the two experimental factors across the whole HBR response, we performed a two-way repeated-measures ANOVA for each time point of the average HBR. The factor hand position was a significant source of variance within the 30- to 98-ms time window (i.e., the HBR was significantly larger in the near than in the far condition; see time course of \(F\)-values in Fig. 3), and particularly in the second part of the HBR waveform (i.e., between 65 and 88 ms). In contrast, the factor recording side was a significant source of variance only in the early part of the HBR waveform (i.e., the HBR was significantly larger at the ipsilateral than at the contralateral recording side within the 44- to 66-ms time window; Fig. 3). The interaction between these two factors across time was not significant \((P > 0.05);\) Fig. 3).

Experiment 2

Effect of hand position and recording side on onset latency and duration of the HBR without vision. Similarly to what was observed when participants had their eyes open (experiment 1), when they had their eyes closed the onset latency of the HBR was shorter in the near \((43.3 \pm 4.6\) ms) than in the far \((45.6 \pm 4.4\) ms) condition, and when the stimulated hand was ipsilateral \((43.7 \pm 4.2\) ms) than contralateral \((45.2 \pm 4.8\) ms) to the recording side. This resulted in a significant main effect of hand position \([F_{(1,7)} = 27, P = 0.001, \eta^2 = 0.79]\) and recording side \([F_{(1,7)} = 11.45, P = 0.012, \eta^2 = 0.62]\) on the HBR onset (two-way, repeated-measures ANOVA). The interaction between the two factors was not significant \((P = 0.71)\).

In addition, the duration of the HBR was longer in the near \((62.7 \pm 13.4\) ms) than in the far \((51.8 \pm 8.9\) ms) condition, and at the ipsilateral \((59.4 \pm 10.5\) ms) than at the contralateral \((55.1 \pm 9.9\) ms) recording side. There was a significant main effect of hand position \([F_{(1,7)} = 7.7, P = 0.027, \eta^2 = 0.52]\), and recording side \([F_{(1,7)} = 6.3, P = 0.040, \eta^2 = 0.47]\) on the HBR duration (two-way, repeated-measures ANOVA). The interaction between the two factors was not significant \((P = 0.18)\).

Effect of hand position and recording side on HBR magnitude without vision. Also similar to what observed in experiment 1, when participants had their eyes closed, the HBR magnitude was larger in the near condition \([near: 173 \pm 57, \text{far: } 101 \pm 39\) AUC arbitrary units; \(+94.8 \pm 116.2\%];\) main effect of hand position, \(F_{(1,7)} = 12, P = 0.011, \eta^2 = 0.63];\) and when the stimulated hand was ipsilateral to the recording side \([ipsilateral: 153 \pm 37, \text{contralateral: } 121 \pm 45\) AUC arbitrary units; \(+37.6 \pm 41\%];\) main effect of recording side, \(F_{(1,7)} = 9.42, P = 0.018, \eta^2 = 0.57].\) The interaction between the two factors was not significant \((P = 0.14)\).

Effects of hand position and vision on HBR magnitude across time. To investigate the possible effect of vision on the HBR across time, and whether and at what time point vision modulated the effect of hand position, in the eight participants of both experiments 1 and 2, we computed a two-way, repeated-measures ANOVA for each time point of the average HBR response. The factor hand position was a significant source of variance of the EMG activity before and after

\[ \begin{align*}
\text{Effect of hand position,} & \quad F_{(1,7)} = 55.1, P = 0.001, \eta^2 = 0.71, \\
\text{Effect of recording side,} & \quad F_{(1,7)} = 9.42, P = 0.012, \eta^2 = 0.63, \\
\text{Interaction,} & \quad F_{(1,7)} = 11.45, P = 0.012, \eta^2 = 0.62.
\end{align*} \]
the HBR, i.e., the background EMG activity was significantly larger in the eyes closed condition within the 14- to 27-ms and 152- to 220-ms time windows (Fig. 4), as expected because of the motoneuronal facilitation during the voluntary contraction caused by eye closure. The interaction between the two experimental factors across time was not significant ($P > 0.05$).

**Experiment 3**

Even when the proximity of the hand to the face was manipulated by rotating the head, i.e., while keeping both the hand and the arm in the same position all the time, the HBR was significantly enhanced ($+96.5 \pm 67.9\%$) when the stimulated hand was inside the peripersonal space of the face [$t(8) = 2.92, P = 0.03$; paired $t$-test]. To investigate the time course of such effect, we performed a paired $t$-test for each time point of the average HBR response. The factor "head position" was a significant source of variance of the reflex waveform within the 58- to 90-ms time window ($P < 0.05$; Fig. 5).

**Experiment 4**

In striking contrast with what was observed in experiments 1–3, hand position did not modulate either the onset latency [far: $38.7 \pm 5.7$ ms, near: $38.3 \pm 5.6$ ms; $t(8) = 0.8, P = 0.46$] or the duration [far: $48.4 \pm 15.2$ ms, near: $49.3 \pm 16.1$ ms; $t(8) = -0.51, P = 0.63$] of the R2 response of the BR elicited by the electrical stimulation of the supraorbital nerve. Also, the magnitude of the R2 was similar in the two experimental conditions [far: $281 \pm 32$, near: $269 \pm 24$ AUC arbitrary units; $t(8) = 0.38, P = 0.72$] (Fig. 6).

**Experiment 5**

Furthermore, hand position did not affect the amplitude [far: $1.85 \pm 0.57 \mu$V, near: $1.83 \pm 0.63 \mu$V; $t(8) = 0.28, P = 0.79$] or the latency [far: $19.9 \pm 2.1$ ms, near: $19.9 \pm 2$ ms; $t(8) = -0.41, P = 0.69$] of the N20 wave of the SEPs measured at scalp electrode C3, contralateral to the side of the stimulation (Fig. 7).

**Discussion**

Our results show that the HBR is influenced by the proximity of the stimulated hand to the face. We observed four main findings. First, when the hand is placed inside the area of peripersonal space surrounding the face, the HBR has shorter onset latency, longer duration, and greater magnitude than when the hand is placed outside this area. This finding indicates that (1) the brain stem circuits mediating the HBR undergo tonic top-down modulation, in that their excitability is increased when the stimulated hand enters the peripersonal space surrounding the face. Second, such HBR enhancement has a similar magnitude when the participants have their eyes closed. This finding suggests that (2) this effect relies on the proprioceptive information about stimulus location with respect to the face. Third, the effect of hand position on the HBR is observed when the proximity of the hand to the face is manipulated either by changing the position of the arm (while keeping the head position constant), or by rotating the head (while keeping the arm position constant). This finding rules out that (3) the HBR enhancement relies on the different proprioceptive input from the stimulated arm. Fourth, neither the BR elicited by the stimulation of the supraorbital nerve or the N20 of the SEPs elicited by median nerve stimulation are affected by hand position. This finding indicates that the enhancement of the HBR is mediated by a selective preactivation of the brain stem circuits subserving the HBR, and not by facilitation of facial motoneurons or by presynaptic disinhibition of primary afferents of the hand.

**Characteristics of the HBR**

We observed that 60% of the subjects participating in our study had a reproducible HBR, i.e., a proportion considerably higher than that reported in previous investigations in healthy volunteers (e.g., 42.8% in Miwa et al. 1998; 27.3% in Alvarez-Blanco et al. 2009). This is likely to be due to the higher stimulation intensity we applied. The same reason might explain why we did not observe the previously reported habituation of the HBR after repeated stimulation (Fig. 1, right). Although Miwa et al. (1995), recording from a number of muscles (including the orbicularis oris, sternocleidomastoid, posterior neck, and pectoralis major), have demonstrated that the HBR is different from a startle reaction, they did not completely rule out that it could still represent the initial part of a startle response. Our observation of a clear lack of habituation of the HBR provides further evidence that the HBR is fundamentally different from a startle response.

Other features of the HBR recorded in the present study (Figs. 1 and 2) are similar to what has been previously reported, e.g., an onset latency of ~45 ms and an earlier onset, longer duration, and greater magnitude in the orbicularis muscle ipsilateral to the stimulated hand. Furthermore, using a novel statistical approach to analyze each point of the HBR, we showed for the first time that the latter effect is limited to the first part of the response (Figs. 2 and 3).

**Effect of Hand Proximity to the Face**

The BR elicited by electrical nerve stimulation has been reported to be more frequent (Miwa et al. 1995; Miwa et al. 1998) and larger (Alvarez-Blanco et al. 2009) when stimuli are applied to the upper limb than to the lower limb. It has been suggested that stimuli applied to the lower limb are less effective in eliciting a clear BR because they trigger less synchronized afferent volleys due to the longer peripheral distance (Alvarez-Blanco et al. 2009). However, from these studies, it cannot be determined whether the distance of the stimulated body part from the face in external spatial coordinates may also modulate the occurrence and magnitude of this response. Here we show that the HBR is dramatically affected by the proximity of the stimulated hand to the face, being enhanced when the hand is located in the peripersonal space surrounding the face (Figs. 1–5). This finding is important, as it indicates that the excitability of subcortical neural circuits, entirely located in the brain stem and mediating a basic defensive reflex, undergo significant top-down modulation from the neocortex.

Converging evidence from behavioral, neuropsychological, and neuroimaging studies supports the view that the location of somatosensory stimuli is initially encoded in a somatotopic frame of reference (i.e., relative to the skin surface) and then automatically remapped into an external, egocentric frame of reference after the relative position of the body parts is taken...
into account (Azanon and Soto-Faraco 2008; Kitazawa 2002; Röder et al. 2004). Studies in both human and nonhuman primates propose that frontoparietal cortical areas, such as the PZ in the precentral gyrus and the VIP area, and their human homologous, are responsible for such remapping (Azanon et al. 2010; Graziano and Gross 1995; Lloyd et al. 2003). Furthermore, this frontoparietal network is thought to subserve the multisensory representation of peripersonal space (Fogassi et al. 1996; Lädavas et al. 1998; Macaluso and Maravita 2010), as well as to respond to aversive visual stimuli presented within the peripersonal space, including stimuli representing potential threats to others (Avenanti et al. 2005; Costantini et al. 2008; Lloyd et al. 2006). Here, given that the HBR, like the R2 component of the trigeminal BR, entirely relies on subcortical circuitry (Cruccu et al. 2005; Leon et al. 2011; Miwa et al. 1996), our finding suggests that these higher order association areas, involved in the transformation of spatial coordinates and in the detection of aversive stimuli delivered in the peripersonal space, preset the brain stem circuits underlying the HBR to be more responsive when the stimulated body part is located inside the peripersonal space surrounding the face. Such increased responsiveness of the brain stem circuits would facilitate the transmission of the signal to the facial motoneurons, resulting in an HBR of shorter latency and larger magnitude when the hand is near the face, and thus a more efficient defensive response. These results provide the first evidence for a top-down modulation of the HBR.
Proximity of the stimulated hand to the face enhances specifically the BR elicited by hand stimulation. Indeed, the R2 component of the trigeminofacial BR was not dependent on hand position (experiment 4). This finding, besides providing further evidence that the circuits for the two reflexes are functionally independent, rules out the possibility that the effect of hand position on the HBR is due to a change of excitability of either the motoneurons innervating the orbicularis oculi muscle or the circuit mediating trigeminofacial BR. Thus the effect could be mediated by a selective disinhibition of the first synapse of the Aβ afferents from the hand, which activate the brain stem circuits subserving the HBR. An alternative possibility is that the neocortex selectively increases the excitability of the subset of brain stem interneurons responsible for integrating the afferent information arising from the hand placed inside the peripersonal space of the face and projecting to the facial nucleus in the pons. The finding that the N20 wave of the SEPs, which represents the first arrival of the Aβ pathway to the cortex (Mauguiere et al. 1999), was not affected by hand position (experiment 5) indicates that the latter possibility is most likely, as it shows that the top-down modulation of the HBR must take place after the first synapse of the lemniscal pathway in the cuneate nucleus (Fig. 8).

Functional Heterogeneity of the HBR

The effect of hand position was stronger in the second part of the HBR (Fig. 3). Together with the observation that the effect of recording side was exclusively present in the first part of the response (Fig. 3), this finding suggests that the HBR is not a unitary physiological phenomenon, but it is mediated by a complex circuit that has two functionally distinct components, undergoing differential modulation. Indeed, the early recording side effect is likely due to an intrinsic anatomo-physiological property of the reticular bulbopontine circuit projecting to the facial nucleus, where a higher number of synapses is necessary to reach the nucleus contralateral to the stimulated side. In contrast, the top-down hand position effect observed across the whole HBR (and stronger in its later part, Fig. 3) is likely to be explained by a cortical projection on the HBR reticular interneurons. Thus we suggest that two physiologically distinct populations of neurons subserve these two experimental effects.

Effect of Hand Position on the HBR Persists in Absence of Vision

The HBR was significantly increased when the stimulated hand was close to the face, even when participants kept their eyes closed (Fig. 4). This finding might seem in contrast with previous studies that have shown that vision of the body is crucial for proprioceptive localization (van Beers et al. 1999) and attentional selection (Sambo et al. 2009), and, furthermore, that external frames of reference used for localizing somatosensory stimuli are dominated by vision (Eimer 2004; Röder et al. 2004). However, it is possible that the absence of current visual information does not suppress the effect of hand position on the HBR because our study did not involve a fine discrimination of the stimulus location and the stimulated hand in space, and the participants had previously seen the two postures.
Conclusion

We show that the HBR is dramatically enhanced when the stimulated hand enters the peripersonal space of the face. Importantly, such effect is mediated by tonic and selective top-down modulation from higher order cortical areas involved in the representation of peripersonal space on the interneurons of the brain stem circuits subserving the HBR. These results are important as they provide compelling evidence that the nervous system is able to adjust its output in a very specific and fine-grained manner, even at the level of seemingly stereotyped defensive reflex responses. These findings are entirely in line with Sherrington’s theory of reflexes as the result of integrated activities of the nervous system and support the existence of a defensive peripersonal space representing a safety margin advantageous for survival (Plaghki et al. 2010).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


