

The effect of facial expressions on peripersonal and interpersonal spaces

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Abstract Identifying individuals' intent through the emotional valence conveyed by their facial expression influences our capacity to approach-avoid these individuals during social interactions. Here, we explore if and how the emotional valence of others' facial expressiveness modulates peripersonal-action and interpersonal-social spaces. Through Immersive Virtual Reality, participants determined reachability-distance (for peripersonal space) and comfort-distance (for interpersonal space) from male/female virtual confederates exhibiting happy, angry and neutral facial expressions while being approached by (passive-approach) or walking toward (active-approach) them. Results showed an increase of distance when seeing angry rather than happy confederates in both approach conditions of comfort-distance. The effect also appeared in reachability-distance, but only in the passive-approach. Anger prompts avoidant behaviors, and thus an expansion of distance, particularly with a potential violation of near body space by an intruder. Overall, the findings suggest that peripersonal-action space, in comparison with interpersonal-social space, is similarly sensitive to the emotional valence of stimuli. We propose that this similarity could reflect a common adaptive mechanism shared by

these spaces, presumably at different degrees, for ensuring self-protection functions.

Introduction

Identifying others' intention through the emotional valence conveyed by their facial expression represents an essential component of our social life (Ekman, 1999; Keltner, Ekman, Gonzaga, & Beer, 2003). Facial expressions are highly informative, mediate visuo-perceptual, psychophysiological and automatic behavioral responses (Vuilleumier & Pourtois, 2007). Facial expressions that communicate cooperation (e.g., happiness) would prompt approaching behaviors, whereas facial expressions that communicate threat (e.g., anger) would induce avoiding behaviors (Marsh, Ambady, & Kleck, 2005). Therefore, emotional stimuli trigger approaching-avoiding reactions that reveal evolutionary adaptations rooted in basic survival mechanisms (Damasio, 1999; Darwin, 1872; Ekman, 1999; Graziano & Cooke, 2006). In agreement with this, neurofunctional evidence has reported activations of the amygdala, the insula, and the prefrontal areas with emotional stimuli generating affective states and adaptive behaviors (Jabbi & Keysers, 2008; Kennedy, Gläscher, Tyszka, & Adolphs, 2009; LeDoux, 2003; Nomura et al., 2004). Moreover, facial expressions remain detectable also in absence of conscious visual processing (hemianopsia) due to striate cortex lesions, thereby showing that even unseen fear stimuli can activate the amygdala via a colliculo-pulvinar pathway (de Gelder, Vroomen, Pourtois, & Weiskrantz, 1999).

Overall, facial expressions, as emotional signals conveying information about individuals' intent, have a strong impact on our capacity to regulate social interactions (Darwin, 1872; Knutson, 1996).

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In proxemics, interpersonal space is the optimal social distance from conspecifics. Typically, this distance increases in uncomfortable/threatening situations and decreases in comfortable/safe situations (Gessaroli, Santelli, di Pellegrino, & Frassinetti, 2013; Hall, 1966; Hayduk, 1983; Kennedy et al., 2009; Tajadura-Jiménez, Pantelidou, Rebacz, Västfjäll, & Tsakiris, 2011).

Research about peripersonal space has demonstrated that social information may also modulate the representation of the space surrounding our body (Brozzoli, Gentile, Bergouignan, & Ehrsson, 2013; Taffou & Viaud-Delmon, 2014; Tajadura-Jiménez, Pantelidou, Rebacz, Västfjäll, & Tsakiris, 2011; Teneggi, Canzoneri, di Pellegrino, & Serino, 2013; for reviews Coello & Iachini, 2015; Lloyd, 2009). Peripersonal space is the within arm reaching area where objects are represented in terms of deployable actions (Berti & Frassinetti, 2000; Farné, Iriki, & Ladavas, 2005; Rizzolatti, Fadiga, Fogassi, & Gallese, 1997). It is also conceived as a *safety buffer zone* protecting our integrity by prompting defensive/avoidance actions (Coello, Bourgeois, & Iachini, 2012; de Vignemont & Iannetti, 2015; di Pellegrino & Ladavas, 2015; Graziano & Cooke, 2006).

An important issue in the neurocognitive debate concerns the nature of the space near the body and, in particular, the extent to which social and sensorimotor spaces share common mechanisms. One way to address this issue is to compare peripersonal and interpersonal spaces to clarify whether they show a similar or different size in response to social information. Recent studies, through Immersive Virtual Reality (IVR), compared two classic paradigms of neurocognitive (*reachability-distance*: distance at which people perceive a stimulus as reachable) and proxemics (*comfort-distance*: distance people prefer from other persons) domains (Iachini, Coello, Frassinetti, & Ruggiero, 2014; Iachini, Coello, Frassinetti, Senese, Galante, & Ruggiero, 2016). Participants determined reachability and comfort distances from virtual confederates/objects while standing still (passive) or approaching them (active). Both distances shrank with humans as compared to objects (Iachini et al., 2014). Moreover, both distances were affected by age and gender effects, i.e., decreased with children and females as compared to adult males, thus reflecting, respectively, affiliative and attraction mechanisms (Iachini et al., 2016; see also Aiello, 1987; Argyle & Dean, 1965; Uzzell & Horne, 2006). Finally, both distances were smaller, and of similar extent, in the active (i.e., when they could decide when stopping their own approaching movement) than passive (i.e., when they could only stop the confederate's movement) condition. These results suggest that both spaces are affected by the approach condition and by basic social information.

A subsequent study showed that even a high-level social mechanism such as moral evaluation can modulate these

spaces (Iachini, Pagliaro, & Ruggiero, 2015a). More specifically, moral evaluations showed a strong and clear impact on comfort distance in both passive and active approaches: the size of this social space decreased when virtual confederates were evaluated as moral and increased when they were evaluated as immoral. Notably, there was an effect of moral evaluations on reachability distance in the passive, not active, condition. When still people observed another person approaching them and described as immoral, there was an expansion of peripersonal space. This increase in response to a social situation perceived as threatening would suggest a common defensive function of the two spaces.

Overall, these studies would support the idea that peripersonal and interpersonal spaces share a common motor nature and are sensitive, at different degrees, to social information. However, it is not yet clear which social mechanisms, and how deeply, affect peripersonal space. Since emotional signals have a fundamental role in social regulation mechanisms (see Damasio, 1999), the question arises as to what extent facial expressions may affect peripersonal-action space along with interpersonal-social space. To our knowledge, they have never been compared to assess whether they are similarly sensitive to others' emotional expressions. Such a comparison may contribute to clarify the role of the protective functions attributable to both spaces during social interactions.

Participants determined *reachability-distance* and *comfort-distance* while approaching or being approached by male/female virtual confederates exhibiting angry, happy and neutral facial expressions. By means of IVR technology, we could keep under control and maintain constant across trials the visual appearance and the way of moving of virtual confederates. One could criticize the validity of IVR studies due to supposed discrepancies between psychological processes in virtual and natural contexts (Hebl & Kleck, 2002; Lampton et al., 1995; Loomis et al., 1999; Rolland et al., 1995; but see Armbrüster et al., 2008; Slater, 2009). However, a recent study comparing human/human and human/virtual-confederate interactions showed similar effects (Iachini et al., 2016). This further supports virtual reality as a valid tool for assessing proxemics behavior in social interactions (Bailenson, Blascovich, Beall, & Loomis, 2003).

We expected an effect of emotional information and approach conditions on both interpersonal-social and peripersonal-action spaces. Considering the link between emotion, action and spatial behavior (Damasio, 1999; Marsh et al., 2005), happy faces should favor approach behaviors and thus smaller distances, whereas angry faces should favor avoidant behaviors and thus larger distances. Emotional expressions could have a different weight in the two spaces. Interpersonal comfort boundary by definition

reflects the emotional quality of social interactions (Aiello, 1987; Hall, 1966; Hayduk, 1983). Therefore, emotional cues should strongly modulate the size of this space by eliciting an expansion in response to negative situations and a contraction in response to positive situations in both passive and active approaches. The peripersonal reachability boundary is defined as an action space and as a defensive space for avoiding threatening stimuli in the immediate action context (di Pellegrino & Làdavas, 2015; Graziano & Cooke, 2006; Rizzolatti et al., 1997). This space should be particularly sensitive to the most threatening condition, i.e., the combination angry-expression plus passive-approach (Adams, Ambady, Macrae, & Kleck, 2006; Marsh et al., 2005; van Dantzig, Pecher, & Zwaan, 2008). If in this condition we observe an increase of peripersonal, along with interpersonal, boundaries we should conclude that the defense in response to a potential social danger represents a fundamental shared function of the space around the body.

Finally, an important aspect of our social life is the empathic disposition toward others (Davis, 1983), and a link between empathic and spatial mechanisms has been suggested (Erle & Topolinski, 2015). Hence, we used the Interpersonal Reactivity Index (Davis, 1983) to see whether the spatial behavior was associated with the individual empathic disposition.

Method

Participants

Thirty-four right-handed students (17 women), aged 19–29 years ($M_{\text{age}} = 23$; $SD = 2.8$), were recruited in exchange for course credit. Participants had normal/corrected-to-normal vision, handedness = 91.1, $SD = 1.9$ (Oldfield, 1971). Nobody claimed discomfort or vertigo during the IVR experience and reported being aware of the experimental purpose.

Setting and apparatus

The experimental setting and the virtual scenario were similar to those of previous studies (Iachini et al., 2014, 2016). The IVR equipment was installed in a $5 \times 4 \times 3$ m room of the Laboratory of Cognitive Science and Immersive Virtual Reality (CS-IVR, Dept. Psychology). The equipment included the 3-D Vizard Virtual Reality Software Toolkit 4.10 (Worldviz, LLC, USA) with the Sony HMZ-T1 (SONY, Japan) head mounted display (HMD) having two OLED displays for stereoscopic depth (images = 1280×720 ; 60 Hz; 45° horizontally, 51.6° diagonally). The IVR system

continuously tracked and recorded participant's position (sample rate = 18 Hz) through a marker on the HMD. Head orientation was tracked by a three-axis orientation sensor (Sensor Bus USB Control-Unit, USA). Visual information was updated in real time. A glove with 14 tactile-pressure sensors allowed the participants to “see” and “feel” their arm movements (Data Glove Ultra; WorldViz, USA). Graphic modeling was created through SketchUp Make (Trimble, USA).

Virtual stimuli

The virtual room consisted of green walls, white ceiling and grey floor ($3 \times 2.4 \times 3$ m; Fig. 1). A total of twelve young confederates (half females) with neutral expression were selected among a colony of highly realistic virtual humans and were used for the present study (Vizard Complete Characters, WorldViz; USA). Virtual humans represented male and female adults aged about thirty years wearing similar casual clothes and were perceived as representation of Italian citizens (see again Fig. 1; on this point see Iachini et al., 2014). Their height was 175 cm (males) and 165 cm (females). Their gaze was kept looking straight ahead throughout the trials (Bailenson et al., 2003). Facial emotional expressiveness was obtained by modeling the virtual faces with 3DS Max (Autodesk) following the KDEF free-database (Karolinska Directed Emotional Faces; Lundqvist, Flykt, & Öhman, 1998). Fourteen participants (seven women) rated on a 9-point scale how much the faces presented on the PC appeared happy/unhappy, friendly/threatening, angry/peaceful, and annoying/quite. Following this evaluation, twelve virtual confederates were selected whose facial expressions were: happy (two males

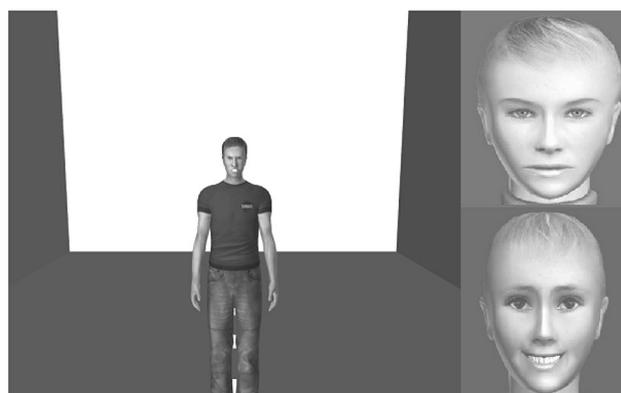


Fig. 1 Examples of virtual stimuli and setting. The *left panel* shows participants' perspective when a virtual male adult with an angry facial expression frontally approached them; on the floor, a straight dashed white line represented the path that participants and virtual humans followed during the passive/active approach conditions. The *right panel* shows examples of neutral (*top*) and happy (*bottom*) facial expressions of virtual women

$M = 6.60$; two females $M = 6.52$), angry (two males $M = 7.79$; two females $M = 8.15$), neutral (two males, two females; Fig. 1).

The interpersonal reactivity index (IRI)

The IRI (Davis, 1983) measures on a 5-step Likert-type scale (from “never true” to “always true”) various facets of dispositional empathy through four subscales (7-items each): Perspective Taking, tendency to adopt the psychological point of view of others (e.g., “I sometimes try to understand my friends better by imagining how things look from their perspective”); Fantasy, tendency to identify with a fictional character (e.g., “After seeing a play or movie, I have felt as though I was one of the characters”); Empathic Concern, tendency to experience feelings of sympathy and compassion for unfortunate others (e.g., “I often have tender, concerned feelings for people less fortunate than me”); Personal Distress, tendency to experience discomfort in distress situations (e.g., “Being in a tense emotional situation scares me”).

Procedure

After completing the IRI scale, participants were instructed about the task, invited to wear the HMD, the Data Glove and to freely explore the virtual room. Through the HMD, participants were fully immersed in the virtual room where they could see the virtual stimuli and could make extensive exploratory movements. Data Glove was used only during this initial training session to allow participants to perceive their arm fully stretched in the virtual scene. During this initial experience, they had to describe their feeling of presence. Next, they were led to the starting location and were provided with a key-press device held in their dominant hand. The experimental session comprised four blocks, administered in a counterbalanced order: passive-comfort, active-comfort, passive-reachability, active-reachability. The comfort-distance instruction was: “press the button as soon as the distance between you and the confederate makes you feel uncomfortable”. The reachability-distance instruction was: “press the button as soon as you can reach with your hand the confederate”. This was repeated in both approach conditions. In the passive-approach condition, participants stood still and saw the virtual confederates walking towards them (0.5 ms^{-1}) until they stopped them by button press. In the active-approach condition, the virtual confederates remained motionless and participants walked towards them (0.5 ms^{-1}) until they stopped and simultaneously pressed the button, after which returned to the starting position. After button press, virtual confederates disappeared. At the beginning of each block, participants received a four-trial training session. The

experimental flow included the task instructions (5 s), a fixation cross (300 ms), and afterwards one virtual confederate appeared (3 m from the participant). Within each block, the IVR system selected six virtual confederates (half female) showing happy/angry/neutral facial expressions. Each virtual confederate appeared 4 times (quasi-randomized order) resulting in 24 trials per block (tot. = 96 trials across all four blocks). Each block lasted about 9 min. A 5 minute break was introduced every two blocks with the HMD taken off. After each block, the experimenter checked whether the participants performed the task correctly. Finally, participants evaluated their experience with the virtual confederates. They reported they clearly identified their facial expressions as if they were “realistic persons”.

Data analysis

In each trial, the participant-confederate distance (cm) was recorded. The mean distances were analyzed through two separate ANOVAs on each Comfort and Reachability task. A 2×3 repeated-measure ANOVA with two factors was used: approach (active, passive) and facial expression (happy, angry, neutral). Data points outside $M \pm 2.5 \text{ SD}$ (.09%) were discarded. The Tukey post hoc test was used. The magnitude of significant effects was expressed by partial eta-squared (η_p^2). Pearson one-variable list correlation analysis was performed on mean distances of the four Approach-Task conditions as a function of the three emotions and mean scores of the four IRI sub-scales.

Results

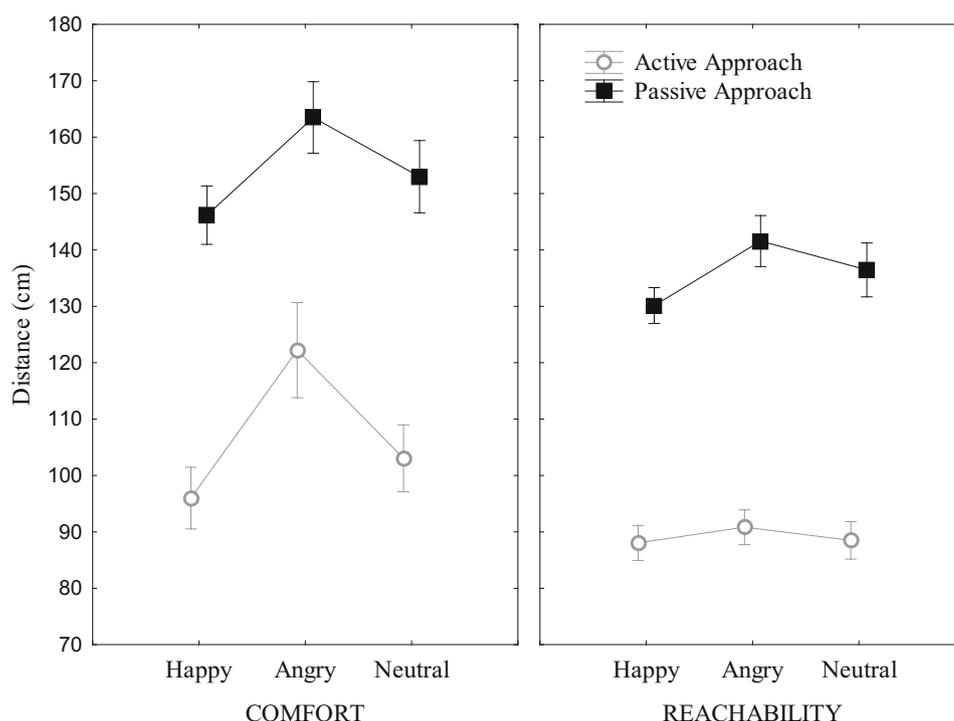
The effect of approach and facial expression conditions is shown in Fig. 2.

Comfort task

A main effect of facial expression ($F(2,66) = 21.402$, $p < .001$, $\eta_p^2 = .39$) showed that spatial distance was larger with Angry ($M = 142.86 \text{ cm}$, $\text{SD} = 43.11 \text{ cm}$) than Neutral ($M = 128.01 \text{ cm}$, $\text{SD} = 35.98 \text{ cm}$) and Happy ($M = 121.08 \text{ cm}$, $\text{SD} = 31.04 \text{ cm}$) faces. All comparisons were significant (at least $p < .001$). A main effect of Approach appeared, $F(1,33) = 78.035$, $p < .001$, $\eta_p^2 = .70$, due to a larger distance in Passive ($M = 154.21 \text{ cm}$; $\text{SD} = 34.84 \text{ cm}$) than Active ($M = 107.09 \text{ cm}$; $\text{SD} = 38.57$) condition.

Approach and facial expression significantly interacted ($F(2, 66) = 3.758$, $p < .05$, $\eta_p^2 = .10$) (see Fig. 2). In the active approach, comfort-distance was larger when seeing an angry than neutral or happy facial expression ($p < .001$).

Fig. 2 Mean (cm) of reachability-distance and comfort-distance for passive and active approach modalities as a function of happy, angry and neutral facial expressions. Error bars represent the standard error



The comparison happy vs neutral facial expression did not reach the significance level (only a tendency, $p = .09$). In the passive approach, comfort-distance was larger when seeing an angry than neutral or happy facial expression ($p < .001$). The comparison happy vs neutral facial expression did not reach the significance level ($p = .10$).

Reachability task

A main effect of facial expression appeared ($F(2,66) = 8.570$, $p < .005$, $\eta_p^2 = .21$). The Tukey post hoc test showed that spatial distance was larger with Angry ($M = 116.20$ cm, $SD = 22.18$ cm) than Happy ($M = 109.09$ cm, $SD = 18.29$ cm) faces ($p < .001$), and only a tendency with Neutral faces ($M = 112.48$ cm, $SD = 23.61$ cm, $p = .08$) emerged. A main effect of Approach appeared, $F(1,33) = 186.814$, $p < .001$, $\eta_p^2 = .85$, due to a larger distance in Passive ($M = 136.05$ cm; $SD = 24.27$ cm) than Active ($M = 89.12$ cm; $SD = 18.46$ cm) condition. Approach and facial expression significantly interacted ($F(2, 66) = 3.090$, $p = .05$, $\eta_p^2 = .09$). In the active approach, no significant differences emerged. Instead, in the passive approach reachability-distance was larger when seeing an angry than happy facial expression ($p < .001$), see Fig. 2.

Correlation analysis

In the Active-approach, as regards Comfort-distance the more participants rated themselves as being empathic with

other people (Empathic Concern) the closer they approached happy ($r = -.34$, $p = .05$) and neutral (only tendency, $r = -.31$, $p = .07$) virtual confederates; as regards Reachability-distance, the more participants reported a tendency to identify with fictitious characters (Fantasy) the farther they approached happy ($r = .44$, $p = .008$) and neutral ($r = .42$, $p = .012$) virtual confederates. In the Passive approach, a negative correlation between Comfort-distance and Personal Distress emerged: the more participants reported a tendency to depression the less they allowed happy ($r = -.34$, $p = .05$) and neutral (only tendency, $r = -.30$, $p = .08$) people approaching them. The Perspective Taking sub-scale showed no significant correlation with the spatial behavior.

Discussion

In this study, for the first time, interpersonal-social and peripersonal-action spaces were compared to assess the influence of emotional facial expressions during dynamic social interactions. We aimed at clarifying if these spaces were similarly sensitive to the emotional meaning of stimuli, and if possible common mechanisms were attributable to protective functions linking spatial-action processes.

The results showed an effect of emotional facial expressions on both spaces. As expected, this effect was particularly strong on interpersonal-social space: comfort-distance was larger with angry than happy or neutral

expressions. Importantly, the emotion effect also emerged in peripersonal-action space, but only the happy vs angry comparison was significant. This would demonstrate that both spaces are sensitive, at different degrees, to the emotional valence of stimuli.

However, the effect of emotional expressions was mediated by approach conditions. Within each space, participants kept larger distances when they could not move than when they could. This confirms that the motor approach condition has a critical role in spatial regulation mechanisms (Iachini et al., 2014, 2015a, 2016). In interpersonal-social space there was an increase of distance from angry as compared to happy and neutral virtual confederates in both passive and active approaches. In peripersonal-action space distance from virtual confederates was larger when seeing an angry than happy facial expression only in the passive approach, not in the active one. Therefore, the effect of emotions was particularly strong in comfort space and appeared in both spaces in the passive-approach when virtual confederates looked angry. This confirms the hypothesis that the defense in response to a potential social danger represents a fundamental function of the space around the body, when declined both in peripersonal and interpersonal terms.

The increase in response to angry approaching confederates may represent the automatic avoidance reaction to the violation of the near body space, as a consequence of arousal regulation and the necessity to ensure a stable self-protection (Dosey & Meisels, 1969; Hayduk, 1983; Siegman & Feldstein, 2014). The need of maintaining a feeling of safety and controlling the motor approach is particularly cogent when the angry person who invades our space is perceived as potentially harmful (Graziano & Cooke, 2006; Horstmann, 2003; Iachini et al., 2015a; Kennedy et al., 2009; Seidel, Habel, Kirschner, Gur, & Derntl, 2010).

The clear anger-avoidance link is consistent with neurofunctional and behavioural studies showing that negative stimuli yield stronger effects than positive stimuli (Cacioppo, Priester, & Berntson, 1993; Cole, Balcetiis, & Dunning, 2013; de Gelder et al., 1999; Öhman, 1987; Strack & Deutsch, 2004; van Dantzig et al., 2008; Vuilleumier & Purtois, 2007). According to an evolutionary perspective, in order to survive it is more important to avoid potentially noxious stimuli, such as predators or other aggressive conspecifics, than to approach positive stimuli, such as smiling conspecifics. Therefore, avoidance mechanisms are among the most important biological adaptations evolved to ensure the survival of the organisms (Adams et al., 2006; Darwin, 1872; Hediger, 1955; van Dantzig et al., 2008). Instead, when other persons communicate positive feelings, we tend to approach them to facilitate the social interaction (Ekman, 1999; Seidel et al., 2010). This suggests that approach and avoidance reactions

reflect the optimal arousal regulation and the necessity to ensure an adequate self-protection barrier around us (Adams et al., 2006; Dosey & Meisels, 1969; Marsh et al., 2005). As soon as we identify and locate an aggressive animal, the motor system reacts quickly by activating an avoidance motor plan. Thus, from an evolutionary point of view, preserving the integrity of our body by quickly escaping from dangerous situations represents a primary adaptive need. Emotional signals during social interactions, thus, help us to anticipate others' intentions by regulating spatial distances around us (Knutson, 1996; see also Gallesse, Keysers, Rizzolatti, 2004). However, while the interpersonal comfort space should represent a social pre-alert margin of potential spatial violations, the peripersonal action space should represent a safety margin more sensitive to the immediate contact/action context.

Moreover, the spatial behavior was associated with the empathic disposition (Davis, 1983; Erle & Topolinski, 2015). Reachability distance increased with higher tendency to identify with fictitious characters: this suggests that individuals who are prone to live in a fantasy world are less willing to approach others. Presumably, this reflects the behavior of introverted people who often prefer taking shelter in a fantasy world and avoid getting in touch with real people. This points to a role for individual personality differences that deserves further studies (see Iachini, Ruggiero Ruotolo, Schiano di Cola, & Senese, 2015b). Not surprisingly, comfort distance shrank as empathic consideration toward others increased, but enlarged (especially from happy confederates) with higher rates of depression. This suggests that interpersonal space is more associated with emotional aspects, whereas peripersonal space is more associated with imaginary-cognitive aspects (Iachini et al., 2015b).

Finally, one could except that the effect of emotional expressions on reachability-distance could simply reflect a carryover effect from the comfort-distance judgment. To control this potential spurious effect, we devised a block-design paradigm administered in a counterbalanced order. We analyzed possible order effects in previous and current studies (e.g., Iachini et al., 2014) and we never found significant effects.

Conclusions

The nature of the space near the body and, in particular, the extent to which social and sensorimotor spaces share common mechanisms represents a relevant issue bridging neurocognitive and social psychology domains. So far, the possible effect of various variables on peripersonal and interpersonal spaces has been investigated, and a complex picture is emerging. For instance, some works have found

substantial similarities (e.g., modulation by social information, action possibility, trait anxiety, moral evaluation Iachini et al., 2014, 2015a, b, 2016; Quesque et al., 2016; Teneggi et al., 2013). Instead, other works using low level sensorimotor manipulations have found selective differences (Patané, Iachini, Farné, & Frassinetti, 2016; for reviews Cléry et al., 2015; De Vignemont & Iannetti, 2015). The present results show that the boundaries of peripersonal-action space, similarly to interpersonal-social space, increase in the most threatening situation, i.e., when participants could not control the motor interaction (passive-approach) while facing angry confederates. This leads us to conclude that the defense in response to a potential social danger represents a fundamental adaptive function of the space around the body when declined both in peripersonal and interpersonal terms. This function is expressed by approach-avoidance actions as driven by the emotional meaning of stimuli. Therefore, spatial behavior, emotional valence and action represent three closely interwoven aspects, as proposed by an embodied perspective of social cognition (Barsalou, 2008; Coello & Iachini, 2015; Niedenthal, Barsalou, Winkielman, Krauth-Gruber, & Ric, 2005). In this perspective, perception and action must cooperate for encoding the distance and socio-emotional meaning of stimuli, and preparing adequate motor reactions.

Compliance with ethical standards

Funding This study was not supported by grant or funding.

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the present study involving healthy participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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