Beyond Unpleasantness. Social exclusion affects the experience of pain, but not of equally-unpleasant disgust

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Abstract

Seminal theories posit that social and physical suffering underlie partly-common representational code. It is unclear, however, if this shared information reflects a modality-specific component of pain, or alternatively a supramodal code for properties common to many aversive experiences (unpleasantness, salience, etc.). To address this issue, we engaged participants in a gaming experience in which they were excluded or included by virtual players. After each game session, participants were subjected to comparably-unpleasant painful or disgusting stimuli. Subjective reports and cardiac responses revealed a reduced sensitivity to pain following exclusion relative to inclusion, an effect which was more pronounced in those participants who declared to feel more affected by the gaming manipulation. Such modulation was not observed for disgust. These findings indicate that the relationship between social and physical suffering does not generalize to disgust, thus suggesting a shared representational code at the level of modality-specific components of pain.

Introduction

When our friends kick us out from a party, we feel excluded. This elicits a complex feeling accompanied by stress, negative mood, but also suffering similar to pain. In this perspective, being left out is simply *disagreeable*, or rather *painful*?

Seminal neuroimaging studies suggested that social exclusion and physical pain recruit a partly common representational code, by showing that being rejected by peers activates a widespread neural network (including the cingulate cortex and insula) held to process the sensory and affective properties of the painful experience (Eisenberger, Lieberman, & Williams, 2003; Kross, Berman, Mischel, Smith, & Wager, 2011; Novembre, Zanon, & Silani, 2015), with the activity in some regions correlating positively with self-reported social distress (Eisenberger et al., 2003). Furthermore, developmental investigations showed that when young children suffer pain, they experience stronger distress during the separation from their mother (Bowlby, 1969). In addition, social support could attenuate the suffering associated with terminal diseases and medical interventions (King, Reis, Porter, & Norsen, 1993; Zaza & Baine, 2002). Most importantly, simulating social discrimination (either through a game or bogus personality tests) affects subsequent ratings of a painful experience. Whereas some researches pointed to an hyperalgesic effect of exclusion, with more unpleasant pain reports after being excluded by peers (Bernstein & Claypool, 2012; Eisenberger, Jarcho, Lieberman, & Naliboff, 2006), others reported an hypoalgesic effect (Bernstein & Claypool, 2012; DeWall, C. Nathan & Baumeister, 2006; MacDonald, Geoff; Kingsbury, Rachell & Shaw, 2005). It is still unclear why these studies vary in terms of the direction of their effects, although a modulating factor might be the severity of the distress elicited by the rejection (Bernstein & Claypool, 2012). Overall, despite their differences, these studies converge with pain overlap theories (Eisenberger & Lieberman, 2004; MacDonald & Leary, 2005), by suggesting the existence of a system that detects and reacts to threats from social relationships in the same fashion in which it detects/reacts to threats of physical injuries. In light of these theories, social exclusion is *painful*.

Recent theoretical accounts challenged pain overlap theories, on different grounds. On the one hand, shared neural responses between pain and social rejection might be only apparent, as activity maps from these two experiences could be dissociated when adopting more sophisticated analytical tools (*hyper-specificity* critique – Koban, Kross, Woo, Ruzic, & Wager, 2017; Woo et al., 2014). On the other, it has being pointed out that pain overlap theories may be based on ill-founded inference, as any shared coding between social exclusion and physical pain might not necessarily reflect modality-specific properties of the painful experience. In particular, social exclusion and physical pain could be similar only in terms of supramodal dimensions related to unpleasantness or the salience of the experience (*domain-general* critique – Iannetti & Mouraux, 2011; Iannetti, Salomons, Moayedi, Mourauz, & Davis, 2013). In this perspective, being excluded is not painful, but simply *unpleasant*.

To address this controversial issue, we ran a study in which participants were excluded by peers in a virtual ball-tossing game (Cyberball) and immediately after were exposed to either a painful temperature or a disgusting odour. Critically, pain and disgust were calibrated on individual basis to insure that, despite their qualitative difference, they were perceived as comparably unpleasant. Disgust represents an ideal control for pain: indeed both these experiences are unpleasant, arousing, threat signals for one's survival and elicit behavioural coping responses. Additionally, comparably-unpleasant pain and disgust were associated with both modality-specific and cross-modal (shared) coding, either by behavioural studies (Sharvit et al., 2015) or neuroimaging investigations testing the responses in insula and cingulate (Corradi-Dell'Acqua, Tusche, Vuilleumier, & Singer, 2016). Within this framework, we planned to assess whether social exclusion taps that component of pain which is modality-specific, or shared with a comparably unpleasant disgusting experience.

In particular, pain overlap theories predict that being excluded would affect specifically the subjective experience of pain, without generalizing to the case of comparably-unpleasant disgust. Alternatively, domain-general accounts would argue that being left out should affect the subjective experience of pain and disgust in comparable fashion. To disambiguate between these competing hypotheses, we measured explicit ratings of pleasantness associated with pain and disgust, but also physiological measures such (as cardiac and electrodermal activity, Sharvit et al., 2015), which could reveal also effects of more implicit nature.

Materials and Methods

Power Analysis

This study was built using the same set-up from our previous research (Sharvit et al., 2015), which found that ratings of comparably unpleasant pain and disgust were influenced by expectancy cues both in terms of their supramodal and modality-specific information. The data from this previous study were used to run a power analysis which assessed the minimum number of subjects necessary to identify similar modulations in our paradigm (average correlation among the repeated measures, r=0.47, smallest effect size of interest η_p^2=0.15). Under these specifications, significant effects at $\alpha \leq 0.05$ would be observed with a power $(1 - \beta) \geq 0.95$ in a population of $N \geq 21$. This estimated sample would be as well adequate to detect effects of $\eta_p^2 \geq 0.26$, as described in previous studies assessing the influence of social rejection on subsequent pain ratings (e.g., Bernstein & Claypool, 2012). The power analysis was run with G*Power 3.1.9.2 software (Faul, Erdfelder, Lang, & Buchner, 2007).

Participants

Our overall population comprehended N=25 participants (16 women; mean age±std 21.12±2.20 y.o., range between 18 and 27). These were selected within a larger group who took part to our experiment. In particular, reminiscently to the case of Sharvit and colleagues (2015, 2018), we included in the analysis only those who did rate pain and disgust as comparably unpleasant in a subset of data independent from those of theoretical interest (Reference Trials, see Results section for more details). Recruitment continued until the minimum number of participants was exceeded. Overall, we tested 30 participants (19 women, mean age±std 21.47±2.97 y.o., range=18-33), 25 of which matched our inclusion criteria. None of the included subjects had psychological/neurological disorders, nor olfactory deficit, nor psychological/neuroscience study background. On average, participants showed no pathological anxiety disorders (on STAI Y-A&B, 40.88±9.57) or pathological depression disorders (on BDI, 4.28±3.53). All participants were naive to the purpose of the experiment and gave their informed written consent. The study was approved by the local ethical committee and carried out in accordance with the Declaration of Helsinki for experiments involving humans. Subjects received a compensation for their participation in the study.

Olfactory stimulation

Odorants were provided by Firmenich, SA (Geneva) based on previous evaluations (Chrea, Valentin, & Abdié, 2009; Delplanque et al., 2008). *Isovaleric acid* (evoking dirty socks) and *Scarym*ol (evoking sweat), (each one diluted in a solution of odourless *Dipropylene glycol* at four different concentrations [0.1%, 0.5%, 5% and 10%]), were used to elicit different levels of disgust in the participants. In the main experiment, each participant underwent only two odorants expected to elicit *low disgust* (LD, rated about ~ − 0.5 in a scale ranging from +5 [extremely pleasant] to -5 [extremely unpleasant]), and *high disgust* (HD, rated about ~ − 5). These odours were selected, at the individual level, on the basis of a pleasantness-rating task conducted at the beginning of the experimental session (see Appendix A for more details). Additionally *Ariana* (evoking shampoo) was also delivered at a concentration of 10% to provide participants relief from the disgusting odours and to reduce the chances of habituation/sensitization. All odorants were stocked in liquid form in test tubes and were delivered to the participants' nostrils via a rubber mask by a computer-controlled, multi-channel, custom-built olfactometer. A constant air flow of 0.5 bars provided by the olfactometer allowed this diffusion without contaminating the next trial and without additional noise or tactile stimulation in the nose (Ischer et al., 2014).

Thermal stimulation

A computer-controlled thermal stimulator with an MRI-compatible 25 x 50 mm fluid-cooled Peltier probe (MSA Thermal Stimulator–Somedic AB, Sweden) delivered thermal stimulations. The stimulator was placed at the left wrist of participants. As the main experiment was divided into two blocks, the position of the thermode was slightly changed to minimize risks of habituation/desensitization to thermal stimuli. For each participant, we selected two different temperatures that were expected to evoke two different levels of pain, *low pain* (LP, rated about ~ −0.5), and *high pain* (HP, rated about ~ −5). Critically, we chose the two temperatures whose the pleasantness was comparable to that of the two disgusting odours selected for the same participant (see Appendix A for more details about the temperature selection).

Experimental Setup

Task design

We used the well-known virtual ball-tossing (Cyberball) game (Williams, Cheung, & Choi, 2000). Participants were told that they were going to play with two couples of confederates, identified as “A&B” and “C&D”. The game displayed cartoon images of three avatars which were supposed to throw the ball to one another. One avatar was controlled by the participant, whereas the other two were controlled by the confederates. Each gaming session was characterized by 13 iterations between the three players. This number was much smaller than that of previous studies employing the same Cyberball task (e.g. between 40-200; Bernstein & Claypool, 2012; Eisenberger et al., 2006; MacDonald, Geoff; Kingsbury, Rachell & Shaw, 2005; Niedeggen, Sarauli, Cacciola, & Weschke, 2014; Weschke & Niedeggen, 2013) due to the need of employing multiple post-gaming thermal/olfactory stimulations (see below). Unknown to participants, confederates’ behaviour was pre-programmed in order to follow two separate profiles (factor: Social Play). In particular, "A&B" threw regularly the ball to the participant (6 out of 13 iterations, i.e. 46% per each trial), and corresponded to the *Inclusion* condition. Instead, "C&D" interacted minimally with the participant, mostly playing with one another, and corresponded to the *Exclusion* condition. Critically, in 50% of the *Exclusion* trials "C&D" passed the ball to the participant only once (out of 13 iterations, i.e. 7%), in 35% of the trials twice, whereas for the remaining 15% of the trials they completely ignored the participant. This variation was introduced to minimize regularities in the game structure, and strengthen the belief of interacting with human confederates. Please note that these parameters are more extreme than those of previous studies, to compensate for the short duration of each gaming session, in which participants had no time to slowly realize the different behavioural pattern of the other players. Appendix B provides validation data of these parameters on independent samples of participants.

Each Cyberball trial started with an introductory screen (2 sec) informing about the couple of confederates participants were about to interact with (e.g., "you are going to play with A & B"). This was followed by 13 iterations (throws) between the avatars that lasted approximately 30 sec. Furthermore, the time spent by each confederate at throwing the ball was randomly ranging between 0.9-2.6 sec, which represented a plausible response time of a human confederate. Once participants received the ball, they could throw it back at one of the two other players at their own pace, by pressing the one of two keyboard keys at their hands' reach. At the 13th game interaction, a 0.8 sec fixation cross was presented on the screen, followed by a 1.5 sec visual cue depicting a human nose or an arm. These stimuli were taken from the revised Snodgrass object pictorial dataset (Rossion & Pourtois, 2004), and were informative about an upcoming olfactory or thermal stimulation. In particular, nose cues were predictive of either a LD or HD olfactory stimulation, whereas arm cues were informative of a LP or HP thermal stimulation (differently from Sharvit et al., 2015, cues were not predictive of the pleasantness of the upcoming stimulus). Next, thermal and olfactory stimuli were delivered consistently with an instructed-sniff paradigm (Delplanque et al., 2009; Sharvit et al., 2018, 2015): participants were instructed to “Breathe-out” during the numerical countdown of 3 sec, and subsequently to “Breathe-in” during the stimulation’s delivery, regardless of whether this was painful or disgusting. Both olfactory and thermal stimulations lasted 2 sec, although for thermal stimuli additional 3 sec were necessary to reach the plateau temperature. After the stimulation, participants had to rate the level of pleasantness of the stimulation on a visual analog scale (VAS) ranging from "extremely unpleasant" to "extremely pleasant". Participants had maximum 5 sec for delivering a response with directional keys of the keyboard, which was subsequently recoded as a scalar ranging from -5 (extremely unpleasant) to +5 (extremely pleasant), and 0 referring to the middle of the scale. Finally, a 1 sec fixation cross appeared on the screen before the start of the next trial (see Figure 1).

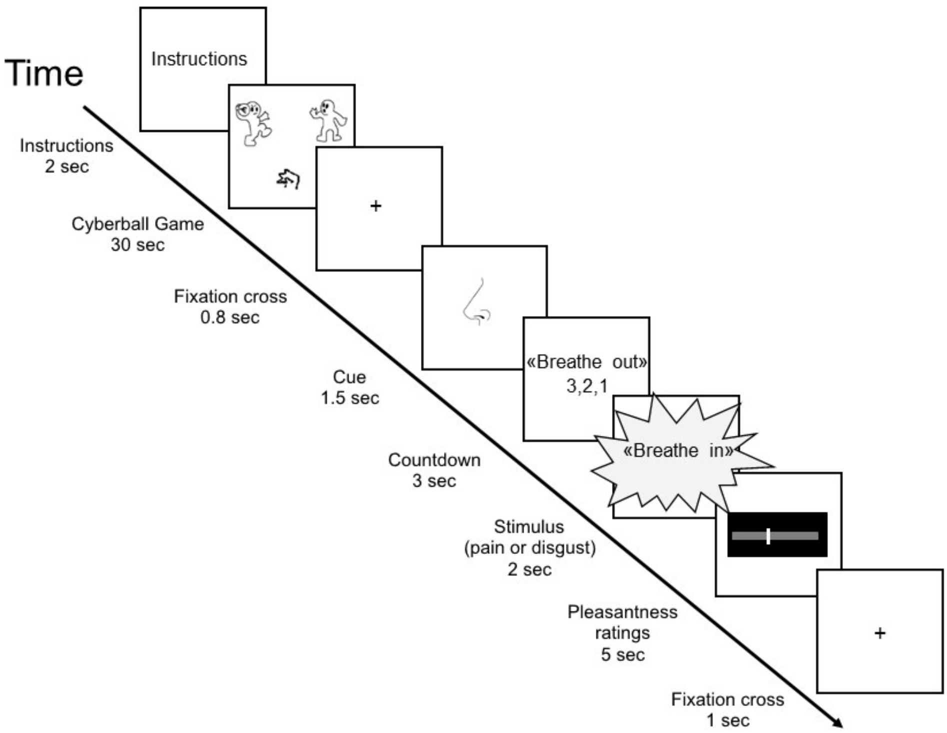

Figure 1. ***Trial structure.*** *Each trial started with the presentation of the instructions for 2 sec, informing the identity of the players of the upcoming game iteration. Subsequently, participants played the Cyberball game for 30 sec. Then, a black fixation cross appeared for 0.8 sec, and one pictorial cue was presented for 1.5 sec, predicting only the modality of the upcoming stimulus (thermal or olfactory). Participants were instructed to "breathe-out" during a 3 sec countdown and then to "breathe-in" during the stimulus delivery – which could be either olfactory or thermal, consistently with the previous cue. All stimuli lasted 2 sec (additional 3 sec were necessary for thermal stimuli to reach the target temperature). Stimuli were followed by a visual analog scale for pleasantness ratings for a maximum of 5 sec. Finally a black fixation cross appeared for 1 sec.*

The task was organized in two blocks. Each block included 16 Cyberball trials, in which each combination of stimulus (LD, HD, LP, HP) and Social Play (*Inclusion*, *Exclusion*) were repeated twice. These 16 Cyberball trials were intermingled with 10 Reference trials (2 trials for HP, LP, HD, LD and positive), in which thermal/olfactory events were presented without any prior playing period. The resulting 26 trials (16 Cyberball + 10 Reference) were presented in pseudo-random order, constrained in such way to prevent more than three subsequent HP or HD stimulations. Finally, in addition to the main 26 trials, each block started with two additional introductory Cyberball trials, one for each pair of players, which were followed by LP/LD stimuli. In particular, "A&B" introductory trial represented an *inclusion* condition identical to those of the remaining part of the block. Instead in "C&D" introductory trial participant received the ball 5 out of the 13 [38%] iterations. The latter was implemented as condition of no interest (hence, not part of the overall analysis) in keeping with previous studies in which ostracizing behaviour in the Cyberball occurred after few inclusive interactions (see also Bernstein & Claypool, 2012; Eisenberger, Gable, & Lieberman, 2007; Eisenberger et al., 2006, 2003; Masten, 2011). Stimuli presentation was controlled using Cogent 2000 (Wellcome Dept., London, UK), as implemented in Matlab R2012a (Mathworks, Natick, MA).

Procedure

Participants first met four actors (two females and two males) posing as confederates. As part of the cover story, they were told that all 5 players (the participant and the confederates) were about to interact in the virtual ball-tossing game from different computer stations connected online. The fact that the participant (but not the confederates) was tested in a separate psychophysiology laboratory with thermal/olfactory stimulation devices was justified as due to limited resources which prevented to apply the same setting to five parallel stations. To reinforce the credibility of the experimental design, participants and confederates listened together to the instructions and signed the consent form. In this perspective, our implementation of the paradigm is reminiscent of that of the "present" Cyberball from Weschke & Niedeggen (2013), according to which physically interacting with the alleged co-players enhanced the subjective effects evoked by the game.

Once participants seated in the lab-chair in front of a computer screen, they were connected to the olfactometer and thermode, and carried out stimuli pre-selection sessions as described in Appendix A. Subsequently, participants went through the main experimental session (two blocks of about 20 minutes each, intermingled by a pause of about 5 minutes). Finally, they were debriefed by *ad hoc* questionnaires assessing whether the exclusion manipulation was effective. In particular, consistently with Williams et al., (2000), we asked them to rate (a) to how much they felt belonging to the confederates (belongingness), (b) how much they thought being appreciated by the confederates (self-value), (c-d) how much they felt being included and excluded by the confederates, (e) how much they liked the confederates (co-players pleasantness), and (f) how much they thought being liked by the confederates (self-pleasantness). For each item and for each couple of confederates, participants provided a rating ranging from 1 (not at all) to 9 (absolutely). Finally, we asked them to guess, through an open question, which was the goal of this experiment. This last question was aimed at identifying those participants who realized the deceptive nature of the study. The entire experimental procedure lasted about 1 hour and 40 minutes.

At home participants filled two questionnaires: the Beck Depression Inventory (BDI, 13 items, (Beck, Ward, Mendelson, Mock, & Erbau, 1961) and the State-Trait Anxiety Inventory (STAI, 40 items, Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) to rate respectively their level of depression and state anxiety.

Physiological Recordings

Following our previous research (Sharvit et al., 2015), we recorded galvanic skin response (GSR), finger pulse, and nose respiration using the MP150 Biopac Systems (Santa Barbara, CA) with a 1000 Hz sampling rate. To measure the GSR, Beckman Ag-Agcl electrodes (8 mm diameter active area) were filled with skin conductance cream and placed on the left hand of the participant on the palmar side of the middle phalanges of the second and the third fingers. We filtered the signal with a low pass filter of 1 Hz and high pass filter of 0.005 Hz. A photoplethysmographic probe (3.2 cm/1.8 cm, LED type photodetector) was placed on the thumb on the left hand to record the finger pulse frequency. We filtered the signal with a band-pass filter (between 10–30 Hz), detected offline electrocardiographic R waves, and then we converted intervals between heartbeats into heart rate (HR), expressed in beats per minute. Finally, nose respiration was measured through a 2.5 mm tube (interior diameter) that was positioned at the entrance of the participant's right nostril. This tube was added to the mask used to deliver the odours, and it was connected to a differential pressure transducer (TSD160A; ± 2.5 cm H_2O sensitivity range). This allowed to record continuously variations in the nostril airflow and to determine nose breathing patterns across different stimulus conditions. This signal was filtered with a low pass filter of 10 Hz.

For each subject, the time course of each physiological measure was *z*-transformed, down-sampled to 10 Hz, and fed into a first level analysis using the general linear model (GLM) framework as implemented in PsPM 3.0.2 (Bach & Friston, 2013) (http://pspm.sourceforge.net). More specifically, we ran a hybrid design, in which physiological responses associated with the game were modelled with two separate boxcar functions, testing the increase response during the inclusion and exclusion blocks respectively. As for thermal/olfactory stimulations, we estimated the event-related responses of each kind of stimulus (LD, HD, LP & HD) and of each kind of Social Play condition (Inclusion, Exclusion and Reference Trials), through an uninformed finite impulse response (FIR) basis function, ranging from 3 seconds prior to the stimulus delivery (corresponding to the onset of the countdown) to 12 seconds following the stimulus delivery. This choice was motivated by the fact that the current design appeared unsuitable for standard response functions for galvanic/cardiac responses, which are optimized on paradigms in which the stimulus presentation was instantaneous (Bach, Flandin, Friston, &

Dolan, 2009; Paulus, Castegnetti, & Bach, 2016). Instead, our dataset is characterized by slowly-occurring thermal stimulations, as well as by a cued-sniffing event (which alters cardiac responses on top of pain/disgust responses). We believe that the FIR approach is more appropriate for our purposes, as it poses no *a priori* assumption on the dynamics of the response function, and allows us to focus on those time-windows of theoretical interest. In particular, based on the analysis of our previous study implementing similar settings (Sharvit et al., 2015), we defined time windows of interest for GSR the 6-12 sec following the stimulus onset. Instead, for HR we focused on the interval 6-11 sec, which describes a portion of the signal in which sniff-induced cardiac modulation returned to baseline (Delplanque et al., 2009; Sharvit et al., 2015). Finally, for Respiration, literature suggests that inspiratory activity is enhanced following pain (Jafari, Courtois, Van Den Bergh, Vlaeyen, & Van Diest, 2017), something which was found in the reanalysis of the data from Sharvit et al (2015) around ~ 5 sec following the onset of both HP and HD (see Appendix C).

Results

Behavioural ratings

The experiment was carried out under the assumption that high pain and disgust were both perceived as more unpleasant than their corresponding low stimuli with no remarkable difference between the two modalities. To insure such prerequisite, in line with Sharvit et al. (2015, 2018) we excluded those blocks whose overall ratings from the Reference trials were associated with the following characteristics: blocks in which HP or HD were rated almost as neutral (HP≥-1, HD≥-1, in a scale ranging from +5 to -5), or equally/more pleasant than LP and LD (HP≥LP, HD≥LD), and blocks in which LP and LD were experienced as too unpleasant (LP≤-4, LD≤-4). The overall analysis was carried out on a population of N = 25 subjects, subtending an overall of 33 out of 50 blocks (2 blocks per participant*25 participants). Critically, blocks were excluded only based on Reference Trials (in which stimuli were delivered in absence of a preceding game), and not on the basis of the ratings in Cyberball trials, which were the real aim of this study. A repeated measure analysis of variance (ANOVA) on the ratings from remaining blocks with *Pleasantness* (negative vs. neutral), and *Modality* (pain vs. disgust), confirmed a main effect of *Pleasantness* ($F_{(1,24)}$=184.90, p<0.001, η_p^2=0.89; see Figure 2A), reflecting the clear-cut discrepancy between negative and neutral stimuli, and no main effect/interaction associated with the factor *Modality* ($Fs_{(1,24)}$≤1.13, not significant [*n.s.*]).

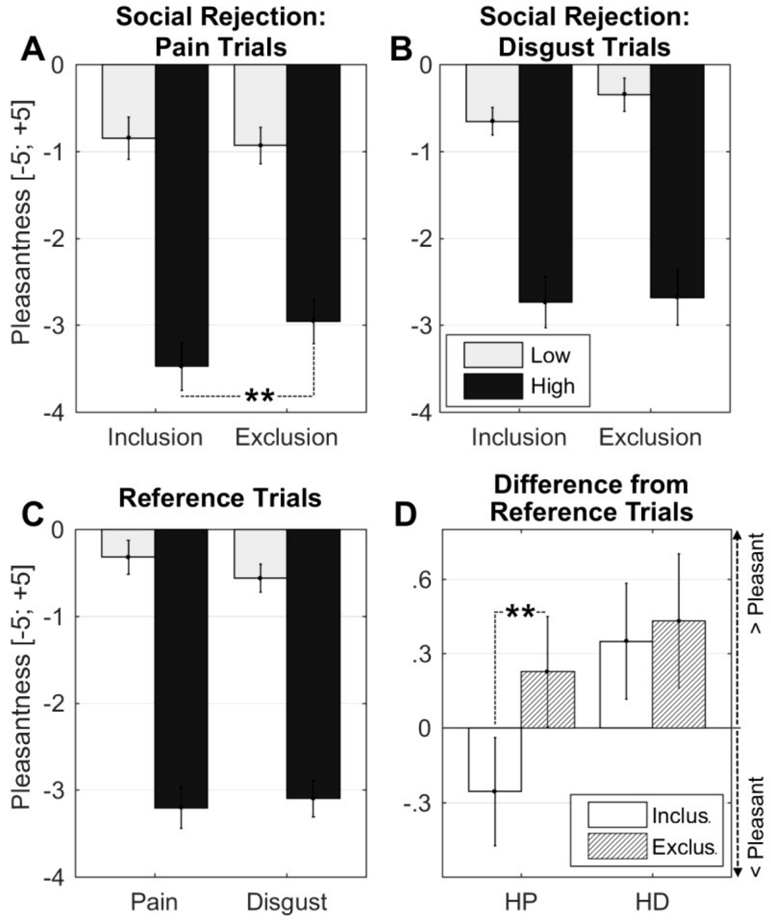

Figure 2. *Pleasantness ratings associated with pain and disgust stimuli. Average pleasantness ratings associated with (A) pain and (B) disgust Cyberball trials and (C) reference trials. Black bars refer to high pain/disgust stimulations, light grey bars to those low pain/disgust. (D) Differential values of high pain and high disgust related to inclusion (white bars) and exclusion (striped bars) from their corresponding values of reference trials(see results).The more values are negative, the less pleasant the experience. Error bars refer to standard errors of the mean. ** refer to conditions eliciting differential pleasantness between the two gaming conditions*

Our main goal was to investigate the impact of social exclusion on participants' subjective experience of comparably-unpleasant painful and disgusting stimulations. To this aim, for each subject and stimulus condition, the median pleasantness ratings from the Cyberball trials were fed to a repeated measure ANOVA with *Pleasantness* (negative *vs*. neutral), *Modality* (pain *vs*. disgust) and *Social Play* (inclusion *vs*. exclusion) as within-subject factors. As for the Reference trials, we found a main effect of *Pleasantness* ($F_{(1,24)}$=121.20, p<0.001,

η_p^2=0.83), indicating that both high pain/disgust were rated more negatively than their corresponding low stimuli. Furthermore, we found a significant main effect of *Modality* ($F_{(1,24)}$=4.62, p=0.042, η_p^2=0.16), a significant main effect of *Social Play* ($F_{(1,24)}$=6.92, p=0.015, η_p^2=0.22), and a significant *Pleasantness*Modality*Social Play* three-way interaction ($F_{(1,24)}$=4.96, p=0.036, η_p^2= 0.17). No other effect in the ANOVA was found to be significant ($Fs_{(1,24)}$≤1.14, *n.s.*). The interplay between *Pleasantness*, *Modality* and *Social Play* was further explored through *post-hoc* Bonferroni-corrected t-tests, examining the effect of *Social Play* in each of the four possible combinations of stimuli (critical p-value 0.05/4=0.012). We found a significant increase in subjective pleasantness (less negative) when high pain stimuli were preceded by the exclusion *vs*. inclusion condition ($t_{(24)}$=-3.35, p<0.003, d=0.67 – see Figure 2B). Instead, no difference between exclusion and inclusion was observed for low pain or for either kind of disgust stimuli ($ts_{(24)}$≤0.41, *n.s.*). Figure 2D displays the differential rating values between HP and HD gaming conditions and Reference Trials, revealing that the Cyberball-induced modulation of HP ratings appears equally characterized by a modulation in the hyperalgesic direction for the inclusion condition (-0.26, S.E.M.: 0.21), and in the hypoalgesic direction for the exclusion condition (0.23, S.E.M. 0.22). Although none of the two gaming conditions are significantly different from the Reference Trials ($|ts|_{(24)}$ ≤ 1.17, n.s.) they are different from one another ($t_{(24)}$=-3.04, p<0.005, d=0.62 – see Figure 2D). Instead, the Cyberball-induced modulation of HD ratings, although not significantly different from the Reference Trials ($ts_{(24)}$ ≤ 1.59, n.s), appear on overall more in the direction of hypo-sensitivity (inclusion: 0.35, S.E.M.: 0.23; exclusion: 0.43, S.E.M.: 0.27), regardless of the kind of interaction experienced during the game. Overall, the analysis of pleasantness ratings suggests that HP alone is modulated by the social treatment received during the game (as described by an inclusion *vs*. exclusion comparison), on top of potential confounding modulations associated with the gaming event *per se* (Figure 2).

Next, we examined whether the effects of social treatment on HP were influenced by the degree with which participants were affected by the manipulation. To achieve this, we took into consideration the self-reports of social distress collected after the experimental sessions. For each of these reports (belongingness, self-value, pleasantness, subjective inclusion/exclusion rating, etc. – see methods section), we took the differential values associated with including co-players (i.e., A&B), relative to the excluding ones (C&D). Indeed, subjects who were the most affected by the paradigm should have reported higher values of belongingness/self-value/pleasantness/inclusion (and lower rates of exclusion) for the inclusive (relative to the exclusive) co-players, whereas subjects who were the least affected by the paradigm should have reported comparable ratings for the two pairs of confederates. These differential values were correlated with the magnitude of the hypoalgesic effect observed in Figure 2A (differential pleasantness ratings for exclusion vs. inclusion HP). As we collected 6 independent self-reports, correlations were considered significant if associated with an α-error ≤ 0.008 (corresponding to 0.5/6 under Bonferroni correction). Under such rigorous threshold, we found a significant effect of Belongingness (Pearson $r=0.58$, $p=0.002$): individuals who felt belonging more to the inclusive (vs. exclusive) confederates were those who in the main task were associated with the strongest hypoalgesic effect (see Figure 3A). No other self-report was associated with significant correlation, although at a more lenient α-error (0.05, uncorrected) a similar effect was observed also for self-value and pleasantness ($r\geq0.44$, $p\leq0.017$, all other reports $|r|\leq0.26$, *n.s.*). The ratings associated with low pain, or high/low disgust stimuli were never significantly correlated with post-experiment self-reports, neither at the most lenient α-errors ($|r|\leq0.24$, *n.s.*).

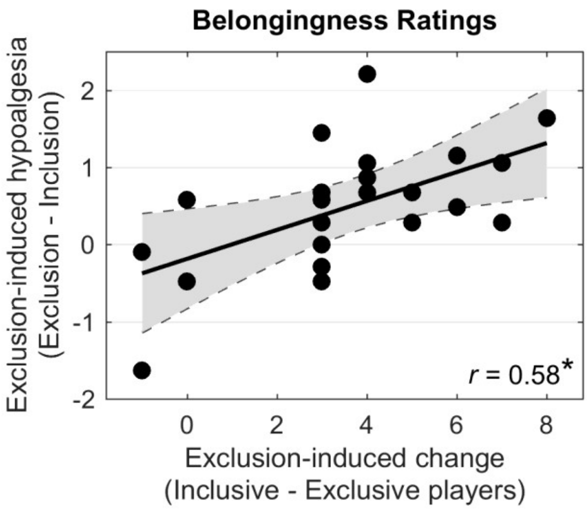

Figure 3. *Inter-individual differences. Magnitude of the exclusion-induced hypoalgesia (differential HP pleasantness ratings for exclusion – inclusion) plotted against exclusion-induced belongingness with the co-players, as measured in post-experimental debrief session. High values in the vertical axis refer to participants who rated HP following exclusion as more pleasant than following inclusion (as shown in Figure 2A). Right values on the horizontal axis refer to participants who felt belonging more to the including co-players, then to the excluding ones, and hence were mostly affected by the manipulation. Left values on the horizontal axis refer to participants who felt belonging to the two pairs of co-players in comparable extent. A linear regression and 95% confidence grey area illustrate the linear dependency between the measures.*

Physiological measures

Among the 25 participants selected for the behavioural analyses, the physiological data of some could not be taken into account due to high amount of artefacts in the signal. Hence, we restricted the analysis to a population of 21 subjects for GSR and respiration and 20 subjects for HR. Figures 4 and 5 describe the event-related changes in GSR, HR and Respiration elicited by the delivery of thermal/olfactory events. Previous studies using the same cued-sniff paradigm (Delplanque et al., 2009; Sharvit et al., 2015) documented that the inspiration event led to a subsequent acceleration of the cardiac response (~ 2-3 seconds from the stimulus onset; Figure 4B in our dataset) followed by deceleration in which valence-related effects became apparent. These previous findings were used to obtain an unbiased estimate of a time-window of interest, in order to ascertain whether unpleasantness-related modulations were indeed influenced by the prior gaming session, in similar or dissociated fashion between pain and disgust. In particular, we considered the collapsed signal from those time-bins which were associated to a significant conjoint effect HP > LP and HD > LD in our previous study (Sharvit et al., 2015, Reference Trials, see Appendix C). These were then fed to the same Repeated Measure ANOVA with *Pleasantness* (negative *vs*. neutral), *Modality* (pain *vs*. disgust) and *Social Play* (inclusion *vs*. exclusion) as within-subject factors.

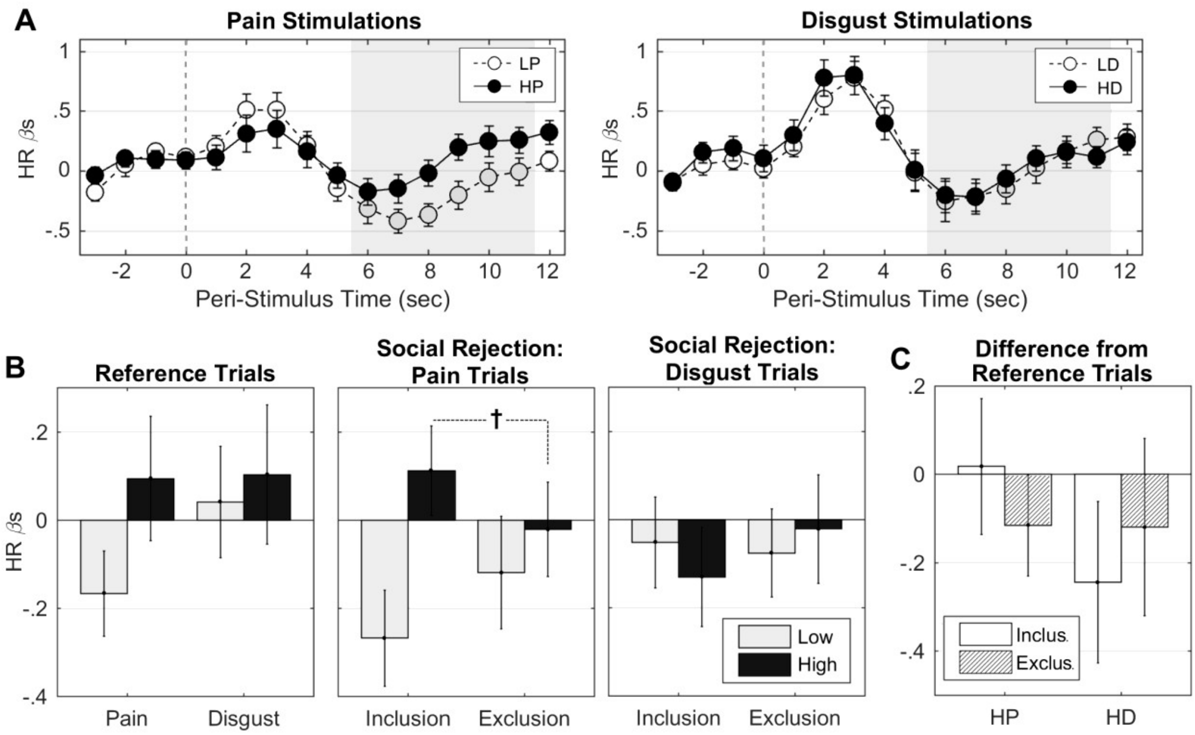

Figure 4. (A) *Event-related change in HR responses associated with comparably unpleasant pain and disgust. Pain data are displayed in the left subplot, whereas disgust data are displayed in the right subplot. Black circles refer to high pain/disgust stimulations, light grey circles to those low neutral controls. Vertical dashed lines, refer to the moment in which the inspiration was cued, and the stimulus delivered. Grey area refers to the time-bins of interest, as mapped in the independent dataset (see Appendix C).* ***(B)*** *Cardiac response within the time-window of interest, associated with reference trials (left subplot), post-gaming pain (middle subplot) and disgust (right subplot) events. Black bars refer to high pain/disgust stimulations, light grey bars to those low neutral controls.* ***(C)*** *Differential values of high pain and high disgust related to inclusion (white bars) and exclusion (striped bars) from their corresponding values of reference trials. Error bars refer to standard errors of the mean. † refer to conditions eliciting differential cardiac response between the two gaming conditions at p (1-tailed) < 0.05.*

More specifically, cardiac responses (time-window of interest: 6-11 sec) were associated with the same *Pleasantness*Modality*Social Play* three-way interaction ($F_{(1, 19)}$=7.44, p=0.013, η_p^2=0.28) as found for the analysis of the behavioural measures (no other effects were found to be significant (Fs≤1.73, *n.s.*). Follow-up *post-hoc* Bonferroni-corrected t-tests, examining the effect of *Social Play* in each of the four possible combinations of stimuli (critical p-value 0.05/4=0.012) revealed no significant effect, although at an uncorrected α value the cardiac response to HP appeared significantly reduced in exclusion following inclusion ($t_{(19)}$ = 1.98, p (1-tailed) = 0.031, d = 0.44; for all other stimuli $|t_{(19)}| < 1.65$, *n.s.*). Figure 4C displays as well the differential values between Reference and Gaming trials, suggesting that HP is associated to a decrease cardiac responses following exclusion, whereas post-inclusion data were broadly similar to that of the Reference trials.

When running the same analysis on GSR (time-window of interest: 6-12 sec) and Respiration (5 sec), we found no significant effect associated with the factor *Social Play*, neither as a main effect or interaction. More specifically, for GSR we found only a Unpleasantness*Modality interaction ($F_{(1, 20)}$=8.44, *p*=0.009, η_p^2=0.30; all other effects Fs≤4.28, *n.s.*), reflecting clear increase of galvanic response to HP (relative to LP), with no corresponding modulation for disgust (see Figure 5A). As for respiration, no significant effect was found (Fs≤1.18, *n.s.*).

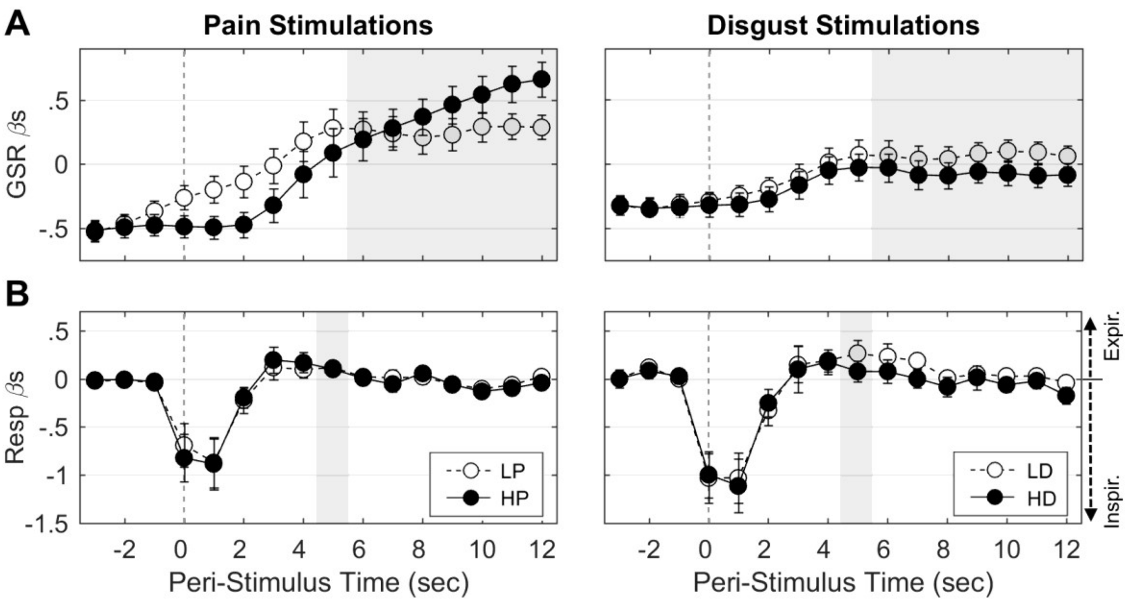

Figure 5. *Event-related change in **(A)** GSR and **(B)** respiration associated with comparably unpleasant pain and disgust. Pain data are displayed in the left subplot, whereas disgust data are displayed in the right subplot. Black circles refer to high pain/disgust stimulations, light grey circles to those low neutral controls. Error bars refer to standard errors of the mean Vertical dashed lines, refer to the moment in which the inspiration was cued, and the stimulus delivered. Grey area refers to the time-bins of interest, as mapped in the independent dataset (see Appendix C). For Respiration, negative values refer inspiratory activity, whereas positive values refer to expiratory activity.*

Discussion

We engaged participants in a gaming experience (Cyberball) in which they were either included or discriminated by confederates. Each game iteration was followed by matched painful or disgusting events. Participants rated painful stimuli as less unpleasant after being excluded (*vs*. included) in the preceding game trial. Such hypoalgesic effect was more pronounced in those subjects who were more affected by the exclusion manipulation, as measured in post-experimental debrief. Consistently, social exclusion decreased also cardiac response to pain. Critically, these effects were not observed if pain was replaced by comparably-unpleasant disgust. Overall, our data suggest that the interplay between social exclusion and physical pain (as frequently highlighted in the literature) does not generalise to other negative experiences. Based on the current findings, the experience of being excluded can be described as more similar to *pain* than to a broad *unpleasantness*.

Social Belongingness and Pain

In our data social exclusion led to a *hypoalgesic* effect compared to inclusion, consistently with previous researches employing both the Cyberball game (MacDonald et al., 2005) or the future-life paradigm, in which bogus personality tests predict a lonesome existence for the subjects (Bernstein & Claypool, 2012; DeWall et al., 2006). Exclusion-induced hypoalgesia has been interpreted in light of models on the relationship between the severity of the injury and the experienced pain. In particular, under heavy physical trauma, in which pain would be excessively strong/long to be endured, regulatory mechanisms are triggered to decrease distress and promote coping strategies (Kandel, Schwartz, & Jessell, 2000). Following this logic, severe social exclusions might as well enhance the same regulatory mechanisms, thus making participants less sensitive to subsequent painful stimulations (Bernstein & Claypool, 2012).

Differently from our case, other studies documented a *hyperalgesic* effect, with higher sensitivity to pain (Eisenberger et al., 2006), especially after a mild social exclusion (Bernstein & Claypool, 2012). In particular, Bernstein and Claypool (2012) pointed that, as for the case of physical pain, when the severity of the rejection is not sufficient to trigger regulatory mechanisms, a summation effect could be observed, with the social distress adding to aching experience. It is possible that specific parametrizations in our paradigm (full within-subject design, extremely polarized exclusion condition, and "present" version of the game characterized by real interaction with the confederates; see methods and Appendix B) might have exacerbated the distress induced by the virtual game. In this perspective, both our set-up and effects are consistent with that of a severe social rejection.

Figures 2D and 4C suggest that, when compared with the Reference Trials, the effects of the Cyberball on HP manifest themselves as both an exclusion hypoalgesia and inclusion hyperalgesia. Furthermore, the modulation observed for HD following both gaming conditions appears more similar to HP in the post-exclusion, than the post-inclusion. We advise caution in comparing directly the ratings from reference and gaming trials, as potential differences could be related, not only to the social manipulation (which is the main interest of the present study), but also to complex visual processing, motor preparation/execution, decision-making, etc.. In this perspective, we believe that our results stem from the combination of two effects, the first due to being engaged in a Cyberball *per se* (game-related effect), and the second driven by the quality of the interaction experienced (social effect). To the best of our knowledge, there are two ways in which game-related and social effects can interact and lead to our findings. First, the gaming session (in both exclusion and inclusion conditions) decreases the sensitivity to any somatic experience, except for post-inclusion HP, which is the only characterized by increased sensitivity. Hence, it is the social inclusion (and not the exclusion) to show a pain-preferential modulation, maybe due to its' overly-inclusive nature (Niedeggen et al., 2014). We feel that this interpretation is unlikely, as it assumes game-related effects on pain to be of hypoalgesic nature, whereas previous studies suggest that being engaged in a cognitively-depleting task should lead to hyperalgesic effects (Silvestrini & Rainville, 2013). Alternatively, game-related and social effects influence each modality separately, with HD possibly desensitized by the Cyberball *per se*, whereas HP being influenced only by the quality of the social interaction, with different directions according to its' inclusive/exclusive nature. According to this latter interpretation, the feeling of social belonging can be described as a linear continuum ranging from extremely exclusive to extremely inclusive (Niedeggen et al., 2014), with each extreme exerting an opposite influence on the subsequent experience of pain.

Keeping these considerations aside, our findings provide clear evidence that the quality of social interactions in the Cyberball (as described by a direct comparison inclusion vs. exclusion) acts on the sensitivity to HP, over and above any potential confounding effects associated with being engaged in a gaming session *per se*.

Domain-General Models

It has been often indicated that interplay between physical pain and social rejection observed in the literature might not necessarily implicate “shared pain” (Iannetti et al., 2013). Pain could be seen as one implementation of a more broad mechanism aimed at detecting (and reacting to) events which are relevant/salient for one's survival. This led to a domain-general account, suggesting that the relationship between pain and social rejection could generalize to any salient event, even painless (Iannetti et al., 2013). Disgust is the perfect control condition for testing such account, as it shares with pain intrinsic unpleasantness, potential obstruction for one's health (related to intoxication/contamination) and consequent coping reactions. In this perspective, our evidence that social exclusion (vs. inclusion) influences individual sensitivity to pain, but not disgust, speaks against this domain-general interpretation.

An alternative model suggests that social rejection may lead to a "deconstructed state", characterized by lack of emotion, lethargy, avoidance of self-awareness and time distortion (Blackhart, Nelson, Knowles, & Baumeister, 2009; Twenge, Catanese, & Baumeister, 2003). Obviously, lethargy and lack of emotion are consistent with a modulation of pain in the hypoalgesic direction as in our study, but would also be consistent (at least in principle) with a similar decreased sensitivity for disgust. Thus, our data do not fit well the idea that the effects of social rejection are at such broad-spectrum. Instead, our findings are better suited for domain-specific interpretations, according to which social exclusion triggers mechanisms involved in processing and regulating pain.

Domain-Specific Models

Pain overlap theories are the most well-known among the domain-specific interpretations of social exclusion, and suggest that being ostracized (often described with terms as "heartbreak", "hurt feelings", etc.) is grounded on the same circuits mediating (and regulating) physical pain (Eisenberger, 2012; MacDonald & Leary, 2005). In particular, the primary function of pain to signal potential body damage might have evolved also to detect threats from social relationships (Panksepp, Nelson, & Bekkedal, 1997). By demonstrating that the quality of the social interaction (social exclusion vs. inclusion), influences the experience of pain in greater extent than the comparably unpleasant disgust, we provide the strongest evidence thus far in favour for this model.

Our data, however, are also open to alternative interpretations, as claiming that social interactions influence pain more than disgust, does not necessarily imply that social exclusion and physical pain share a sensory-specific representational code. For instance, physical pain might underlie processes involved in selecting/promoting coping response of withdraws, potentially present also with the evaluation of social events. This interpretation is in line with appraisal theories of emotions (e.g., Scherer, 2009), arguing that affective responses do not reflect only the sensory-specific properties of a stimulus, but rather how this stimulus is evaluated in terms of implications, significance for the self/community, coping potential, etc.. Thus, shared representational coding between two states might not relate only to sensory-specific information, but also to similar output from specific appraisal checks. Future studies will need to compare systematically the appraisal components associated with noxious stimulations and social belongingness, and how they differ from those related to physical disgust.

Limitations of the study and conclusive remarks

Differently from Sharvit et al. (2015) that used similar settings, here disgusting odours did not elicit enhanced physiological responses relative to control odorants (see also Appendix C). However, our previous experiment differs from the present study in the fact that participants were not aware whether the cued odorant would have been disgusting or not, thus insuring that effects related to unpleasantness were purely bottom-up. It is possible that the bottom-up information was not sufficiently strong to elicit a rapid disgust-related physiological response. Participants might have become aware of the disgusting nature of the stimuli only when subsequently asked to provide a rating.

Furthermore, although our effects were linearly modulated by participants' ratings of belongingness, these reports were collected only at the end of the experimental session, and not after each trial. This choice was necessary given that participants were already engaged in the rating of thermal/olfactory stimuli, and the presence of multiple serial evaluations might have led to sequential biases. It is important to stress that, at least in the case of belongingness, our validation experiment reveals a high compatibility between offline and online ratings (inclusion – exclusion difference: r = 0.63, see Appendix B). This provides support for the fact that offline belongingness ratings (and their effects as depicted in Figure 3) are a reliable proxy for the subjective feeling experienced during the game. However, validation data show also a weak compatibility between online and offline ratings of exclusion (see Appendix B), thus underscoring the need of caution in employing experimental paradigms relying exclusively on offline measures.

Notwithstanding its limitations, our study shows that being excluded (vs. included) affects the subjective experience of pain, without generalizing to the case of comparably-unpleasant disgust. These findings provide stronger support for models of shared representational code between social belongingness and physical pain, than for domain-general accounts positing a role of supramodal dimensions such as unpleasantness or salience. In light of these results, being left out by our friends should not be considered simply a disagreeable experience, but rather a *painful* one.

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Appendixes:

Appendix A: Thermal and Olfactory preselection tasks

In the olfactory preselection task, all 9 odours (plus 10th odourless control) were delivered to the participants as follows: each trial began with a 1 sec fixation cross that was presented in the centre of the computer screen; then the instruction “Breathe-out” was presented together with a numerical 3 sec countdowns. During the countdown, participants were instructed to expire and empty their lungs. When the countdown reached 0, participants had to breath in evenly while the text string “Breathe-in” instruction was presented and the odorant delivered. This trial structure allowed to minimize the intra- and inter participant breathing pattern variability (see also Delplanque et al., 2009; Sharvit et al., 2015) and to synchronize the respiration cycle with the odorant delivery regardless of its nature. After each stimulus, a visual analogic scale (VAS) was presented. Participants were asked to rate the degree of subjective pleasantness evoked by the odorant by marking the corresponding position on the scale with a mouse device held in their right hand. The 10 stimuli (9 odours plus the control odourless solution) were presented twice in an equally distributed and pseudorandomized order. The olfactory-stimuli selection session lasted approximately 15 minutes.

In line with previous studies (e.g. Sharvit et al., 2015), during the thermal preselection task individual temperatures were determined through a modified double random staircase (DRS) algorithm aimed at identifying stimuli of comparable unpleasantness (measured with the same VAS as for the odorants selection session) to the highly unpleasant odour. Our DRS procedure selected a given temperature on each experimental trial according to the previous response of the participant. Trials rated as more unpleasant than the given cut-off (selected in a subject-specific way, from ratings for the highly unpleasant odour) led to a subsequent lowered temperature in the next trial; whereas trials rated as less unpleasant than the given cut-off led to a subsequent higher temperature. This resulted in a sequence of temperatures that rapidly ascended towards, and subsequently converged around, a subjective unpleasantness threshold, which was in turn calculated as the average value of the first 4 temperatures leading to a direction change in the sequence. To avoid participants anticipating a systematic relationship between their rating and the subsequent temperature, two independent staircases were presented randomly. Initial thermal stimulations for the two staircases were 41°C and 43°C. Within each staircase, stimulus temperatures increased or decreased with steps of 3°C, while smaller changes (1°C) occurred following direction flips in the sequence. None of our subjects was stimulated at temperature larger than 52°C. The thermal stimuli were delivered in the following way: participants first saw a 1 sec long fixation-cross, followed by the text string “Temperature is changing” and concomitant delivery of the heat stimulation. Each thermal event was composed of 3 sec of rise time, 2 sec of plateau at the target-temperature, and 3 sec of return to baseline (37°C). The speed of the temperature rise and the temperature return was automatically adjusted according to the plateau in order to maintain both a rise time and a return time of approximately 3 sec each. The pleasantness scale was presented just after the 2 sec of plateau stimulation, when the temperature started to return to baseline, and lasted until participant provided a response. The present DRS approach was employed to determine temperatures eliciting two distinct levels of unpleasantness (corresponding to different levels of pain): low and high. This approach led to a highly unpleasant temperature, which varied on a participant-by-participant basis, but converged around the average value of 47.28C (SD 2.54). Based on this temperature, we selected one additional temperature associated with more neutral ratings, corresponding to an average value of 43.99°C (SD 2.77). This session lasted approximately 10 minutes.

Appendix B: Validation experiments for Cyberball parameters

As our study involved brief gaming sessions (characterized by 13 interactions between the players), we ran an independent study to validate the parameters used in the main experiment, and insure that it was eliciting two clear-cut conditions (social inclusion vs. exclusion) even within such constrained gaming-time. This experiment was characterized by two groups. The first (N = 20 [10 men, age = 25.15, std = ± 4.11]) underwent an experiment which was identical to the main one, with the exclusion condition characterized by participants receiving the ball ~7% of the interactions, and the inclusion condition, with participants receiving the ball ~46% of the interactions. In this condition, participants received the ball with higher frequency than the 1/3 probability, and was reminiscent of the over-inclusive condition used by Niedeggen et al. (2014). The second group (N = 20 [9 men, age = 25.20, std = ± 4.50]) underwent the same kind of experiment, except that in the inclusion condition participants received the ball ~33% of the cases. In both cases, the task was identical to that described in the main experiment, except that no thermal/olfactory stimulations were delivered (neither post-gaming nor in reference trials), and Cyberball sessions were followed by subjective ratings of: (*a*) *belongingness* (in a VAS subsequently converted in value ranging from 1 [not belonging at all] to 9 [totally belonging]); (*b*) *exclusion* (ranging from 1 [not excluded at all] to 9 [totally excluded]); (*c*) *pleasantness* (from -5 [extremely unpleasant experience] to +5 [extremely pleasant experience]); (*d*) *fairness* (from -5 [extremely unfair treatment] to +5 [extremely fair treatment]). Finally, at the end of the task, participants underwent the same debrief session than in the main experiment, including the 9 offline ratings ranging from 1 (not at all) to 9 (absolutely) related to the gaming sessions just performed (e.g., belongingness, inclusion, exclusion, etc.).

Table A1. *Average ratings (plus bootstrap-based 95% confidence intervals) associated with both online and offline ratings in the validation experiment. "Group 1" represents data associated with an "inclusion" condition in which participants received the ball ~46% of the iterations, whereas "Group 2" represents data associated with an inclusion condition in which participants received the ball ~33% of the iterations. Groups differences are displayed as results of two-sample t-tests with significance highlighted as follows: *p < 0.05; **p < 0.01; ***p < 0.001.*

		Group 1 *(46%)*	**Group 2** *(33%)*	**Diff.** $T_{(38)}$
Online Ratings				
Belongingness [1, 9]	*Inclusion*	8.75 [8.39 9.11]	6.52 [5.65 7.29]	**4.89*****
	Exclusion	2.86 [2.22 4.26]	2.42 [1.96 3.02]	0.80
Exclusion [1, 9]	*Inclusion*	2.08 [1.73 2.48]	4.39 [3.60 5.26]	**-4.82*****
	Exclusion	8.01 [6.44 8.81]	8.47 [7.79 8.93]	-0.72
Pleasantness [-5 +5]	*Inclusion*	3.68 [3.15 4.11]	1.14 [0.18 1.98]	**4.81*****
	Exclusion	-2.82 [-3.58 -1.33]	-3.14 [-3.68 -2.44]	0.52
Fairness [-5 +5]	*Inclusion*	3.65 [3.11 4.07]	1.29 [0.34 2.08]	**4.63*****
	Exclusion	-2.75 [-3.51 -1.24]	-3.28 [-3.88 -2.50]	0.80
Offline Ratings				
Belongingness [1, 9]	*Inclusion*	8.05 [7.50 8.40]	6.00 [5.15 6.70]	**4.50*****
	Exclusion	2.15 [1.70 3.05]	2.20 [1.70 2.95]	-0.11
Self-value [1, 9]	*Inclusion*	7.75 [7.10 8.25]	5.65 [4.70 6.45]	**3.86*****
	Exclusion	2.70 [2.05 3.80]	2.95 [2.25 4.05]	-0.40
Exclusion [1, 9]	*Inclusion*	2.20 [1.65 3.45]	4.30 [3.45 5.40]	**-3.22****
	Exclusion	7.50 [6.30 8.20]	6.10 [4.90 7.10]	1.90
Inclusion [1, 9]	*Inclusion*	8.10 [7.31 8.50]	5.95 [5.00 6.65]	**4.26*****
	Exclusion	2.55 [1.95 3.66]	2.35 [1.80 3.10]	0.37
Co-players Pleas. [1, 9]	*Inclusion*	8.00 [7.45 8.30]	5.60 [4.50 6.50]	**4.22*****
	Exclusion	2.30 [1.70 3.35]	2.45 [1.80 3.25]	0.28
Self-Pleasantness [1, 9]	*Inclusion*	8.15 [7.75 8.40]	6.30 [5.30 7.10]	**3.67*****
	Exclusion	2.35 [1.75 3.60]	2.35 [1.75 3.10]	0.00

The table A1 reports the average values and the confidence intervals related to both online and offline ratings, with group differences highlighted. As visible, the two groups differed extensively in terms of the inclusion condition, with Group 1 associated with more extreme, and less variable ratings. No difference was observed in terms of exclusion condition.

Given that belongingness and exclusion ratings were delivered both online and offline, this experiment allowed also to ascertain the compatibility between online and offline measures in capturing the individual variations in task susceptibility. For the case of belongingness, we found strong correlations between offline and online ratings of inclusion (Group 1: r = 0.47, p

$= 0.035$; Group 2: $r = 0.62$, $p = 0.003$), exclusion (Group 1: $r = 0.80$, $p < 0.001$; Group 2: $r = 0.49$, $p = 0.027$), and inclusion – exclusion difference (Group 1: $r = 0.63$, $p = 0.003$; Group 2: $r = 0.66$, $p = 0.002$). Instead, for the case of exclusion, the ratings the correlation was not systematically significant, in neither inclusion (Group 1: $r = 0.28$, $p = 0.235$; Group 2: $r = 0.63$, $p = 0.003$), exclusion (Group 1: $r = 0.28$, $p = 0.234$; Group 2: $r = 0.41$, $p = 0.072$), nor inclusion – exclusion difference (Group 1: $r = 0.19$, $p = 0.420$; Group 2: $r = 0.34$, $p = 0.141$).

Appendix C: Time-window of interest for physiological measures

To obtain an unbiased estimation of the time-bins of interest, we fed an independent dataset characterized by the same thermal/olfactory stimulations (Sharvit et al., 2015, Reference Trials) to the GLM routines used for the present experiment (see methods). Figure A1 displays the event-related change in GSR, HR and Respiration, from the countdown onset to the first 12 seconds following the stimulus delivery. In exploratory fashion, we mapped time-bins characterized by a significant effect of HP (vs. LP) and HD (vs. LD). In particular, for GSR and HR we mapped significant increases of signal for HP & HD in the time between 6-12 sec (GSR) and 6-11 sec (HR). For Respiration, common effects between modalities were observed only around 5 sec following the stimulus onset, and were characterized by increased inspiratory activity (lower values) following HP and HD. At the same time, only for the case of disgust, we found decreased inspiratory activity (higher values) in the 1-2 sec from the inspiration onset. The highlighted differences (partly described already in Sharvit et al., 2015) are consistent with an already established literature suggesting that pain and disgust, not only enhance galvanic/cardiac response, but also affect respiration in an heterogeneous way: by diminishing the inspiratory activity during the delivery of unpleasant odours (see also Sharvit et al., 2018; Delplanque et al., 2009), but by increasing inspiratory during the occurrence of pain (Jafari et al., 2017).

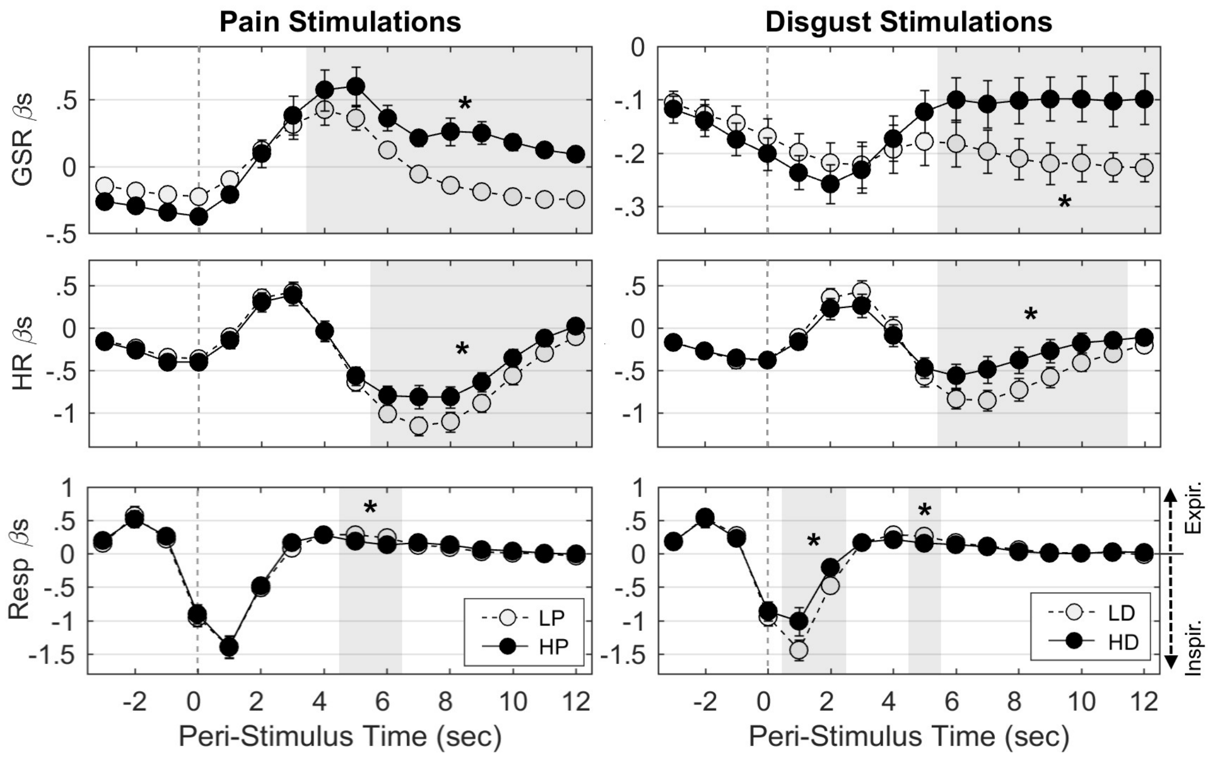

Figure A1. *Event-related change in GSR, HR and Respiratory responses associated with comparably unpleasant pain/disgust (data from Sharvit et al. 2015). Pain data are displayed in left subplots, whereas disgust data are displayed in right subplots. Black circles refer to high pain/disgust stimulations, light grey circles to those low neutral controls. Error bars refer to standard errors of the mean. Vertical dashed lines, refer to the moment in which the inspiration was cued, and the stimulus delivered. Grey area refers to conditions eliciting directional differential effects for unpleasant vs. neutral stimulations at p≤0.05. Specifically, for GSR and HR increased responses for unpleasant are highlighted. For Respiration, for the first 2 seconds following the cued-sniff, decreased inspiration volumes (higher values) for unpleasant odours highlighted as well. For the remaining parts of the time-window, increased inspiration volumes (lower values) for unpleasant stimuli are displayed as well.*

Appendix D: Supplementary Materials

De-identified data files and analysis scripts for this paper are available at Open Science Framework: https://osf.io/zty6r/