Beyond unpleasantness: social exclusion affects the experience of pain, but not of equally-unpleasant disgust

Guyon, Amélie

UNIVERSITÉ DE GENÈVE
FACULTÉ DE PSYCHOLOGIE ET DES SCIENCES DE L'ÉDUCATION

BEYOND UNPLEASANTNESS:

SOCIAL EXCLUSION AFFECTS THE EXPERIENCE OF PAIN, BUT NOT OF EQUALLY-UNPLEASANT DISGUST

MEMOIRE REALISE EN VUE DE L'OBTENTION DE LA

MAÎTRISE UNIVERSITAIRE EN PSYCHOLOGIE

ORIENTATIONS

PSYCHOLOGIE AFFECTIVE

PSYCHOLOGIE COGNITIVE

PAR

AMELIE GUYON

DIRECTEUR DU MEMOIRE

CORRADO CORRADI-DELL'ACQUA

JURY:

GERALDINE COPPIN

KIMBERLY DOELL

GENEVE, AOÛT 2017

UNIVERSITE DE GENEVE

FACULTE DE PSYCHOLOGIE ET DES SCIENCES DE L'EDUCATION

SECTION PSYCHOLOGIE

ACKNOLEDGMENTS

Because I would not have been able to provide this work without social support, I would like to start by expressing my gratitude:

- To Prof. Corrado Corradi-Dell'Acqua who allowed me to be part of the TOPLab and of this research. I thank him for believing in me, for his help and his support.

- To Lia Antico who was constantly present at my side to guide me in the right direction. She receives all my gratitude for her patience, her benevolence and her perseverance. Without her help nothing could have been possible. To Zainab K. Mohamed, my very dear "labpartner" who reminded me that I was not alone to run those experiments. That was a team work and no word could express my recognition for these two women.

- To Gil S. Sharvit who taught me how to conduct this experiment but especially who learned me one hundred ways to crash Matlab.

- To Géraldine Coppin and Kimberly Doell who kindly accepted to be part of the jury.

- To the TOPLab members and especially to Giada Dirupo. Also to Sabrina Totaro who never blamed me for taking her place next to Zainab. I will never forget all those funny moments passed with you.

- To each of our confederates who came sometimes only once and sometimes more: Angela A., Arun C. (especially him who was always there), Chiara C., Eric V., Eugénie C., Francesca D., Jennifer P., Kévin C., Laura R., Sarah D., Timothé M., Yoav H., Yveline H., and all the random person in the BBL who kindly accepted to play the game. I already apologize if I forgot some of them.

- Finally, last but not least, to my friends but mostly to my family who still cannot understand what I am doing at University and who nevertheless continues to love me and supports me in all my adventures. Merci à vous tous!

ABSTRACT

Seminal studies found common activations during social and physical pain and suggested that they were underpinned by the same modality-specific processes. However, recent studies challenged this vision by arguing that those shared activations could be explained alternatively by modality-independent processes and so they could be shared with other unpleasant experiences, as disgust. To better understand those shared processes, we recruited 30 volunteers (M = 21.47 y.o., SD = ± 2.97 y.o.) and asked them to play to a virtual ball-tossing game with four confederates who excluded or included participants in the game. During this task, participants received comparably-unpleasant sensory stimulations (painful or disgusting). We recorded physiological measures and their evaluation of unpleasantness for the sensory stimulation. Our results showed modulations on the physiological measures and a diminution of the reported unpleasantness only for highly painful stimulation after being excluded. This effect was not observed for disgust, suggesting that social exclusion triggers a component of physical pain that is modality-specific.

Keywords: pain; disgust; social exclusion; unpleasantness; cyberball

TABLE OF CONTENT

1 Introduction

This study is at the core of a hot debate that outlines different views regarding the relationship between social exclusion and physical pain. On the one hand, scholars argued that social exclusion and physical pain share the same cognitive processes and neural substrates (Eisenberger, 2003). On the other hand, others challenged these theoretical accounts by arguing that social exclusion and physical pain elicit only apparent overlapping activations (Woo et al., 2014), or they reflect a common representation related to salience/unpleasantness of a given event that is not specific to pain, but common to other aversive emotional states, such as disgust (Iannetti, Salomons, Moayedi, Mouraux, & Davis, 2013).

This research aims at investigating the relationship between social exclusion and physical pain by studying whether and how being excluded by others can influence our sensitivity to physical pain. To do this, we examined how social exclusion can modulate our judgment of pleasantness as our physiological responses to disgusting and physically painful stimulations. We considered that physical and social pain are recruiting a modality-specific representation that is unique for pain and not a supramodal code for properties common to other aversive experiences, such as disgust. Consequently, we predicted that our sensitivity for physically painful stimulation should increase or decrease after being socially excluded whereas it should not be the case for disgusting stimulations.

1.1 What is physical and social pain?

Physical pain is defined as an « unpleasant sensory and emotional experience associated with actual or potential tissue damage » (Mersky & Nikolai, 1994). Indeed, it has been proposed that physical pain is composed of two components: a sensory component and an affective component. The sensory component would make us able to localize and categorize the type and intensity of the painful stimulation, activating the primary (S1) and secondary (S2) somatosensory cortices and the posterior insula (PI). While, the affective component represents the unpleasantness and the motivation that drive us to put an end to the painful stimulation,

activating the anterior insula (AI) and the anterior cingulate cortex (ACC) (See Figure 1). (Apkarian, Bushnell, Treede, & Zubieta, 2005; Price, Harkins, & Baker, 1987; Rainville, Duncan, Price, Carrier, & Bushnell, 1997; Treede, Kenshalo, Gracely, & Jones, 1999).

But whoever has already experienced a break-up or the loss of a loved one will tell us that it is one of the most painful experience that they had to endure, even though there was no tissue damage or potential physical hurt. They will even go so far as to use metaphors referring to physical pain to speak of it, such as: « heartbreak », « hurt feelings ». This phenomenon is not only visible in English language, but also in a lot of culture language around the world (Macdonald & Leary, 2005). It could be a mere linguistic coincidence but a number of works have hypothesized the existence of a relationship between physical pain and what we more commonly call *social pain*.

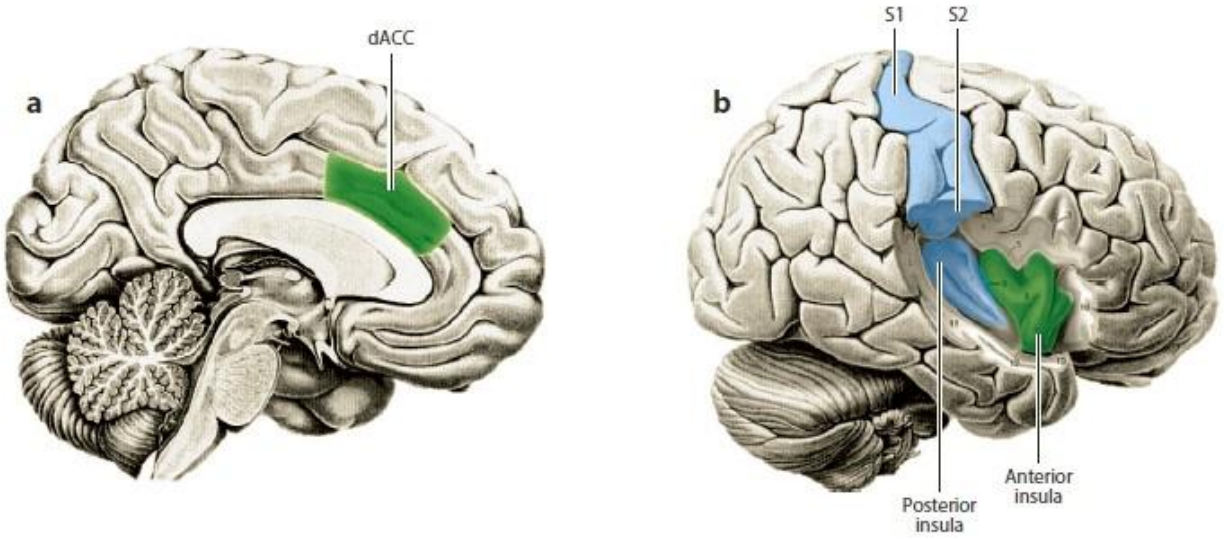

Figure 1. Brain region implicated in physical pain. In blue are represented regions associated to the sensory component (Primary somatosensory cortex (S1), Secondary somatosensory cortex (S2) and Posterior Insula (PI)). In green are represented regions associated with the affective component (dorsal Anterior Cingular Cortex (dACC) and Anterior Insula (AI)). (Eisenberger, 2015)

Social pain has been defined as « the unpleasant experience that is associated with actual or potential damage to one's sense of social connection or social value (owing to social rejection, exclusion, negative social evaluation or loss) » (Eisenberger, 2012). In 2005, Macdonald and Leary proposed the Social Pain Theory, highlighting the growing importance of our need to affiliate with others and the necessity of adaptation to it. Indeed, our attachment system seems to be strongly linked to our exploratory system and our fear system. It means that without a security base (represented by a caregiver at a younger age and a lover later) people will have an increase of anxiety and they will feel distress to find someone to be affiliate with (Sharver, Hazan, & Bradshaw, 1988). Attachment is vital because it provides us access to resources, protection from danger and access to potential mate partners (Brewer & Shapard, 2004). Because of the significance of this attachment, our system would have evolved and would have created the social pain system. At the biological level, Panksepp (1998) argued that instead of creating a totally new system for social pain, we would have updated primitive systems which were already present in our organism: the primitive attachment system, thermoregulation system and more importantly the physical pain system. So, as for physical pain cues, our pain system would have evolved to detect signals indicating potential social exclusion and to help us to react quickly by terminating, reducing or escaping the potential threat (Bowlby, 1973; Macdonald & Leary, 2005). This embodied vision of physical and social pain is supported by a large field of research about social exclusion in neuroscience.

Social exclusion is a form of social pain. It has been defined as a « distressing experience arising from the perception of actual or potential psychological distance from close others or a social group » (Eisenberger & Lieberman, 2004). To induce social exclusion, several paradigms have been used including showing disapproving faces to participants (Kross, Egner, Ochsner, Hirsch, & Downey, 2007), showing participant's ex-partners pictures with whom their romantic relationship ended badly (Kross, Berman, Mischel, Smith, & Wager, 2011), or receiving a negative feedback about a personality test (DeWall & Baumeister, 2006). However, the most used paradigm is the cyberball game task. It was used for example by Eisenberger, Lieberman, & Williams in 2003, asking participants to play at a virtual ball-tossing game with two other participants who were in reality controlled by the computer. In particular, in their experimental design there were three different conditions that create a gradient of exclusion: 1) inclusion (two confederates play with the participant), 2) implicit social exclusion (the participant can watch the

game but cannot participate because of a technical problem invented by the experimenter), and 3) explicit social exclusion (the participant can play but the confederates almost never throw him the ball).

First of all, those paradigms induce a negative mood state and a decrease in self-esteem, in the feeling of meaningful existence, belonging and control (Gonsalkorale & Williams, 2007; Williams, Cheung, & Choi, 2000; Zadro, Williams, & Richardson, 2004). But more importantly, the more subjects felt distressed and excluded, the more they showed an increase of activity in regions known for being implicated in the affective component of physical pain: dorsal Anterior Cingulate Cortex (dACC) and AI (Eisenberger, 2012). Consequently, it has been supposed that only the affective component was shared by social and physical pain, letting us still able to distinguish one pain from the other (Kunz, Peter, Huster, & Lautenbacher, 2013). Even though an overlap of activation has been showed also for the sensory component if the exclusion feeling is strong enough (Kross, Berman, Mischel, Smith, & Wager, 2011).

To go further, it seems that physical pain system and social pain system not only share cerebral activations, but are also regulated by the same opioid neuroendocrine system. Indeed, our nervous system contains μ-opioid receptors (MOR) and endogenous opioids (from the opiate family including opium and morphine) which are known to play an important role in inducing analgesia and/or decreasing physical pain (Kehoe & Blass, 1986; Kehoe & Blass, 1986; Konecka & Sroczynska, 1990). However, it has been highlighted in animal studies, particularly in mice studies, that it would be also the case of social pain. In fact, injection of drugs activating MOR in infant animals reduces social behaviour, such as distress crying when they are isolated from their mother (Carden, Hernandez, & Hofer, 1996; Carden & Hofer, 1990; Kalin, Shelton, & Barksdale, 1988; Kehoe & Blass, 1986; Kehoe & Boylan, 1994; Panksepp, Vilberg, Bean, Coy, & Kastin, 1978). At the opposite, lack of MOR provides less cries call and shows a deficit in attachment behaviors (Moles, Kieffer, & D'Amato, 2004). The opioids impact on social pain has also been reported in human studies (Way, Taylor, & Eisenberger, 2009). Actually, Hsu et al. (2013) showed an increase of MOR activation during exclusion compared to inclusion condition, meaning that MOR would be used to reduce distress. According to Eisenberger (2012), having social connections would induce a reward feeling which could be substituted thanks to the MOR activation. Therefore, opioids could decrease the need of attachment and by extension we could

decrease the social distress linked to social exclusion. In the same way recently, implications of the opioid system in social pain have been highlighted by studies on placebo effects (Koban, Kross, Woo, Ruzic, & Wager, 2017). Placebo effects have been described as "improvements in symptoms caused by treatment cues, expectations, and the psychosocial context in which treatment takes place" (Koban et al., 2017). They observed that the placebo effect decreases painful feelings not only of physical pain but also of social exclusion. Interestingly, they argued that the emotional distress was reduced by altering the affective representations and recruiting a frontal-brainstem network, including dorsolateral prefrontal, rostral anterior cingulate cortex, orbitofrontal, ventromedial prefrontal cortex, and periaqueductal gray.

Finally, it has been hypothesized that if there is a shared use of the same neuronal system, then it should have repercussions on a behavioral level. In other words, if physical pain and social exclusion share the same neuronal system, then they should be able to influence each other. But more precisely, if social exclusion was induced, it could influence physical pain sensitivity. This idea was tested by Eisenberger, Jarcho, Lieberman & Naliboff (2006) who asked their participants to play to the cyberball game and found that in the exclusion condition participants tended to show an increase of sensitivity to physical pain. Dewall & Baumeister (2006) have also tested this idea but, instead of playing the cyberball game, participants filled a personality test and received false feedback about the implications of their personality score related to their future life, such as future relationships. Their results showed an opposite effect compared to that one reported by Eisenberger et al., (2006). Indeed, they found that participants in the exclusion condition tended to show a decrease of sensitivity to physical pain. These opposite results could have led to a debate but Bernstein & Claypool (2012) realized an experiment where they used two versions of the future-life paradigms: one with a severe exclusion and another one with a less severe exclusion. Their results showed a decrease of pain sensitivity after the severe exclusion whereas an increase of pain sensitivity was observed after the less severe exclusion. Consequently, they pointed out that this difference was due to a difference of strength in social exclusion. Meaning that if the exclusion is felt as weak, people would tend to have increasing pain sensitivity but if the exclusion is felt as strong, people would tend to have decreasing pain sensitivity.

1.2 Problematic

Despite all those evidence going to the direction of the Social Pain Theory, numerous criticisms have been made related to the relationship between social exclusion and physical pain. The most important one lied on the implication of ACC and AI emotion processing and especially in negative emotion.

This criticism was born from the observation of Iannetti et al. (2013), who pointed out that maybe this overlapping of activation was only due to the inefficiency of actual techniques as electroencephalography (EEG) or magnetic resonance imaging (MRI) to distinguish two (or more) populations of neurons. In fact, even though the same region could have been activated during two different experiences, it does not mean that the same neurons from the same system in those regions are activated. So, it would be impossible to determine if the activation in dACC and AI during a physically painful stimulation and a socially painful stimulation could be explained by the same population of neurons, as postulated by the works of Eisenberger and colleagues, or two different ones implicated in different networks. The potential answer to this issue would be the use of a multivariate pattern analysis (MVPA), as it has been shown by Woo et al. (2014). Indeed, this method allows a more precise analysis of the activation being able to distinguish the type of neurons by realizing comparison of activation pattern. Their results indicated the existence of two different activation patterns, letting them supposed that there would be not only one but two different systems implicated in pain and social exclusion processing. However, Woo et al. also highlighted that they only investigated the core pain-processing brain system and not the rest of the cortex, indicating that shared activations exist but it would not be pain related. According to Iannetti and Mouraux (2010), this shared activation could be associated to a broadly process as salience, which is « how much a stimulus contrasts with its surroundings along one or more physical dimensions». Indeed, this idea is mainly sustained by Iannetti et al. (2013) who suggested that physical and social pain are "both experiences trigger[ing] multimodal cognitive processes involved in detecting, orienting attention towards, and/or reacting to salient events". Furthermore, they pointed out that physical and social pain would present a common activation not because they are using the same system specific to pain to be processed, but because the two are processed as a salient event because of their unpleasantness. Moreover, Mouraux et al. (2011) have reinforced this hypothesis by founding a similar increase of cerebral activation in dACC

after administering salient nociceptive and non-nociceptive stimulation. Consequently, Corradi-Dell'Acqua, Tusche, Vuilleumier, Singer (2016) wondered if negative emotional experience and physical pain are processed in ACC and AI by a common modality-independent system like unpleasantness or by different systems specific to each modality like pain distress. For this purpose, they compared the brain activation when people felt or saw pain to the brain activation when people felt or saw disgust. The choice to compare pain to disgust rather than another emotion was not a hazard.

In fact, even though pain and disgust are two distinct experiences, they have numerous common points beginning by their function. Pain and disgust are unpleasant emotional states activated when we are in front of an actual or potential danger for our survival (Kunz et al., 2013). Disgust is a reaction to avoid poisoning, whereas pain incites us to avoid risk of body damages. Furthermore, those two emotional states shared a facial expression very similar even though they stay distinguishable thanks to a difference of action unit combination (Kunz et al., 2013) (See Figure 2). In each case, we can notice eyebrow contraction (Action Unit 4), nose wrinkling (AU9), elevation of the upper lips (AU10) and narrowing of the eyes (AU6/7). Finally, those emotional states give rise to similar cerebral activations, not matter if it is seen or felt, (Benuzzi, Lui, Duzzi, Nichelli, & Porro, 2008) and again, it is an increase of activation in ACC and AI.

Corradi-Dell'Acqua's findings (2016) showed that the right part of the AI was more implicated in modality-specific processing of painful and disgusting input, whereas the left part of AI and medium Anterior Cingular Cortex (mACC) take care of modality-specific output integration into a more abstract representation of events. According to this study, there would be two systems implicated in pain and disgust processing, one specific to pain and one processing unpleasantness. But is it also the case for social pain? Is there also a shared modality-specific to pain activation as postulated by Panksepp (1998) or is it a shared activation at the level of an amodal system processing unpleasantness?

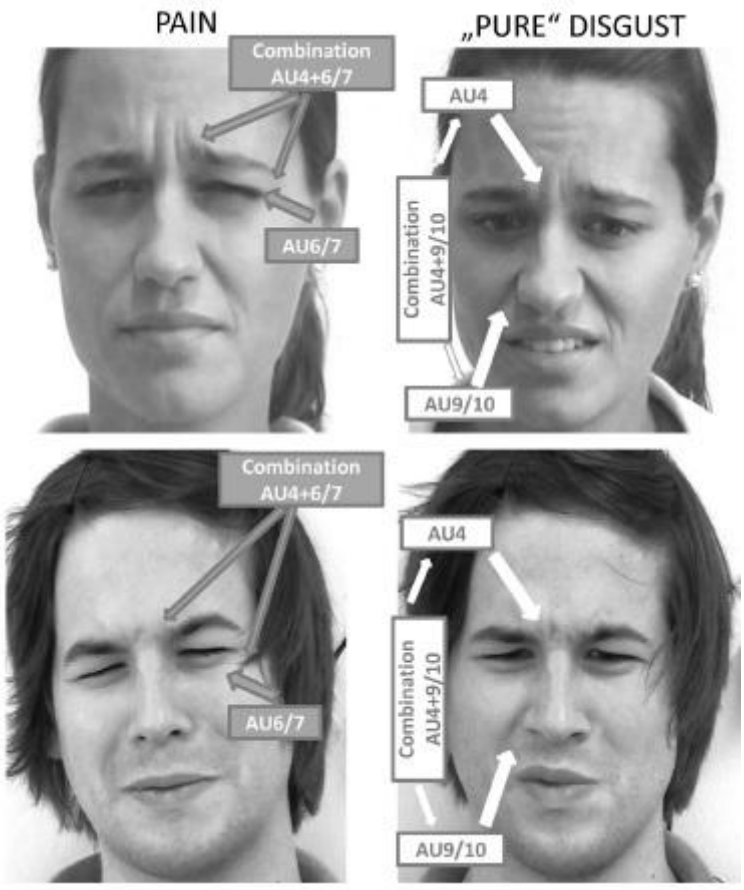

Figure 2. Facial expression of pain and disgust. (Kunz et al., 2013)

In conclusion, up to now, the literature has shown with the Social Pain theory that 1) physical and social pain have a shared neuronal activation in dACC and AI, 2) they are modulated by the same substances and 3) they are able to influence each other. However, the literature also tends to show that ACC and AI activations may be only apparent overlapping activations or they would be more generally related to unpleasantness processing and consequently common to other aversive states, such as disgust. Our research interest is therefore to investigate whether social exclusion is underpinned by processes which are specific to pain or are implicated in unpleasantness in general. To do this, we investigated whether social exclusion can influence our sensitivity to pain but also to disgust. We predicted that our sensitivity for physically painful stimulation would increase or decrease after being socially excluded whereas it would not be the case for disgusting stimulations.

2 Methods

2.1 Participants

In this study, we recruited 30 students (19 woman and 11 men) from the University of Geneva through local ads to participate in psychology experiments. All of them were between 18 and 33 years old (M = 21.47 y.o., SD = ± 2.97 y.o.). They had no psychological or neurological disorders, no olfactory deficit, and no psychological or neuroscience study background. They were non-smoker or light smoker and they had not participated to a similar study on odor before. All participants were naïve to the purpose of the experiment and gave their informed written consent before participating in the study. The study protocol, inclusion criteria, and consent procedure were reviewed and approved by the ethical committee of the University of Geneva. The experiment was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Subjects received a compensation of 42 Swiss francs for their participation in the study.

2.2 Material

2.2.1 Olfactory stimulation

For this experiment, we used four kinds of odors: two unpleasant (*Isovaleric acid*, which smells like dirty socks, and *Scarymol*, which smells like sweat), one pleasant (*Ariana*, which smells like shampoo), and one neutral (*Dipropylene glycol*, which is odorless). The odorous substances were provided by Firmenich, SA (Geneva) and were chosen on the basis of previous evaluations (Chrea, Valentin, & Abdié, 2009; Delplanque et al., 2008; Ferdenzi et al., 2013). Unpleasant odors were diluted in four different concentrations: 0.1%, 0.5%, 5% and 10% and were used to elicit disgust in the participants, whereas the pleasant odor was presented with a concentration of 10% and was used to elicit positively-valenced sensations in the participants, to give them some relief from the disgusting odors and to decrease the chances of habituation/sensitization. Finally, the neutral odor was used as a control. In total, we had 10 odors

to present to participants (See Tables 1). The odorous substances were stocked in liquid form in test tubes and were delivered by a computer-controlled, multi-channel, custom-built olfactometer to the participants' nostrils via a rubber mask. 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).

Table 1

Type of odors and concentration used for this study

Number	Odors	Concentration
1	Scarymol	0.1%
2	Scarymol	0.5%
3	Scarymol	5%
4	Scarymol	10%
5	Isovaleric	0.1%
6	Isovaleric	0.5%
7	Isovaleric	5%
8	Isovaleric	10%
9	Ariana	10%
10	Dipropylene glycol	Control

During the calibration (see Procedure and apparatus below), participants smelled all 10 odors to identify the odorant that was experienced as most disgusting. In each trial, a fixation cross was presented in the center of the screen for 1000ms and later, when the instruction « Breath out » appeared with a numerical countdown of 3000ms, participants were asked to expire. Then, when the countdown reached 0, the instruction « Breath in » appeared and they were asked to inspire while the odor was delivered for 2000ms. This sequence of instruction helped us to decrease the variability pattern of respiration between subjects and to synchronize the respiratory

cycle with the odor's delivery (Delplanque et al., 2009; Sharvit, Vuilleumier, Delplanque, & Corradi-Dell'Acqua, 2015). After each stimulation, participants were asked to rate with a computer keyboard the degree of subjective pleasantness elicited by the odor on a Visual Analog Scale (VAS) going from « Extremely Unpleasant » (-5) to « Extremely Pleasant » (+ 5). To avoid a direction effect, the orientation of the scale was inverted alternatively between subjects, but it was the same for each subject within the entire experiment. All 10 odors were presented randomly twice, but only two unpleasant odors were selected individually for each subject: one to induce high disgust (HD: pleasantness rating ~-4) and the other one to induce low disgust (LD: pleasantness rating ~-0.5).

2.2.2 Thermal stimulation

To induce pain, a computer-controlled thermal stimulator with an MRI-compatible 25 x 50 mm fluid-cooled Peltier probe (MSA, Thermotest) was placed at the left wrist of the participant to deliver different levels of temperature. We used temperatures between 41°C and 52°C.

To determine the pain threshold of each participant, we stimulated them with different temperatures. During each trial, a fixation cross was presented in the center of the screen for 1000ms and then, when the instruction « Temperature is changing... » appeared, the heat stimulation was delivered. Each thermal stimulation took 3000ms of rise time, 2000ms of plateau at the target-temperature and then it went down at the baseline temperature (37°C). Finally, as it was for the odors, participants were asked to rate the degree of unpleasantness of the target-temperatures on the same VAS going from « Extremely Unpleasant » (-5) to « Extremely Pleasant » (+ 5). The temperatures were selected through a modified double random staircase (DRS) algorithm that identified stimuli of comparable unpleasantness to the unpleasant odor (See Corradi-Dell'Acqua, Tusche, Vuilleumier, & Singer, 2016; Sharvit et al., 2015 for similar approaches). In each experimental trial, the DRS procedure designated a given temperature according to the previous response of the participant. When the participant rated trials as more unpleasant than the given cut-off (chosen individually from ratings for the highly unpleasant odor of each subject), the algorithm reduced the subsequent temperature delivered in the next trial,

whereas, when he/she rated trials as less unpleasant than the given cut-off, it increased the subsequent temperature. We presented randomly two independent staircases in order to avoid that the participant anticipated a systematic relationship between their ratings and the subsequent temperature. The two staircases started to deliver a thermal stimulation of either 41°C or 43°C and then they increased or decreased the temperature of 3°C, or specifically of 1°C when the direction flipped in the sequence. Therefore, temperatures fluctuated until they converged around a subjective unpleasantness threshold that was in turn calculated as the average value of the temperatures in the first 4 flips.

Finally, the experimenter used this threshold to determine individually for each subject two unpleasant temperatures: one to induce high pain (HP: pleasantness rating ~-4) and the other one to induce low pain (LP: pleasantness rating ~-0.5). Critically, individually for each subject, the high/low pain temperatures selected had to be rated as equally-unpleasant as high/low disgust. Those operations were repeated twice. Once prior the beginning of the experiment, and the second time after the first half of the experiment was completed. This second thresholding session was run after having modified the thermal stimulation's location.

2.3 Experimental Setup

2.3.1 Pretest

First, subjects were invited for a pretest to assess their sensitivity to our unpleasant odors through a brief session of 10 minutes in which they smelled different odors and rated the degree of their unpleasantness following the same procedure described above for the calibration (see section 2.2.1 Olfactory stimulation). Then, subjects were included in the main experiment if: (i) they rated differently the different odors, (ii) they rated at least one of the odors as unpleasant (below -4), the pleasant odor as pleasant (over 0) and the neutral odor as neutral (around 0), (iii) they were sensitive to different concentrations of the same odorous substances, (iv) their ratings were consistent when the same odors were delivered a second time.

2.3.2 Procedure and apparatus

Our study had two parts: calibration and the main experiment. Participants who had passed the pretest successfully were invited a few days later to take part in the study individually. On the day of the experiment, participants met four others people (two female and two male confederates). They were told that they would have to play a virtual ball-tossing game with them in different laboratories and that they would have been connected online. Unknown to participants, they were going to play actually with a spiteful computer. To reinforce the credibility of the experimental design, participants and confederates listened to the instructions and signed the consent form. As a cover story, experimenters explained that only one laboratory was equipped with the olfactometer and, thus, they separated them in two laboratories: one for the person who passed the pretest, (the real participant), and one for the four other persons (confederates). Once participants were in the laboratory, they had to fill our pre-experiment questionnaires on the computer and, then, they were connected to the olfactometer, thermal stimulator and the biopac (to measure their respiration, electrodermal activity and finger pulse rate).

Next, we carried out olfactory and thermal calibrations before starting the main task. The main experiment was composed of two blocks. During the pause, between the two blocks, we moved the thermal stimulator (still near the left wrist) to avoid thermal habituation and we checked whether their sensitivity to the odors and temperatures that we used during the first block changed and, eventually, we adjusted the olfactory and thermal stimulations for the second block. Finally, after the main experiment, we asked participants to fill our post-experiment questionnaires and we debriefed them. Altogether, this whole procedure lasted about one and a half hour to two hours.

We projected visual stimuli on a PC screen (Dell) on a screen (1024 × 768 resolution) and recorded key-presses on keyboard (Dell).

2.3.3 Cyberball task

This task is a virtual ball-tossing game called Cyberball (Williams et al., 2000). Participants were told that they were going to play with the four people that they met previously, one couple per time (A&B or C&D). Once the game started, they saw the cartoon images of himself/herself and of the other two players on the screen (See Figure 3) and, when they received the ball, they could throw the ball to either the player on the left or on the right by pressing the respective directional keys on the keyboard. Each trial was composed of 13 throws and lasted approximately 30000ms.

Unknown to participants, each couple of people represented an experimental condition. In particular, the couple A&B threw regularly the ball to the participant (6 out 13 throws, i.e. 46 % of the time per each trial) and corresponded to our inclusion condition, whereas the couple C&D poorly interacted with the participant, mostly playing with one another, and corresponded to our exclusion condition. Critically, to boost the credibility of the game, participants received the ball from C&D in the following way: for half of the trials only once, for 35% of the trials twice, and for the rest they never received the ball. In addition, for the same purpose, the simulated players threw the ball with a random delay which ranged between 900 to 2600ms. However, once participants received the ball, they had no limit of time before throwing the ball to the player on the right or on the left.

The task was cut in two blocks with a pause in between. Each block was set for 18 "playing" trials (See Figure 4): one introductory phase that started always with one inclusion and one partial exclusion (5 out 13 throws, i.e. 38% of the trials, that we did not take into account for our analyses), and then the main phase composed of a random sequence of eight inclusions and eight exclusions. After each "playing" trial, a 800ms fixation cross was presented on the screen, followed by a 1500ms cue of a nose or an upper limb to inform participants only about the modality (olfactory or thermal) of the stimulation that they would have received right after. Keep in mind, however, that cues were not informative about the unpleasantness of the upcoming stimuli (high or low). Then, participants were instructed to "Breath-out" during the numerical countdown of 3000ms, and to "Breath-in" during the stimulation's delivery, regardless of whether this was painful or disgusting. Both olfactory and thermal stimulations lasted 2000ms,

although the thermal stimulation reached the target-temperature after 2000ms. Subsequently, participants had to rate the level of unpleasantness of the stimulation on a VAS within at maximum of 5000ms. After the rating, a 1000ms fixation cross appeared on the screen before the start of the next trial. In total per each inclusion/exclusion condition, participants received twice the same stimulation in a random sequence, in which there were no more than three subsequent highly painful or highly disgusting stimulations. In addition, to check whether there was no habituation to the odors or temperatures used and to assess that participants felt high stimulations as more unpleasantness than low stimulations, we introduced eight "reference" trials per block (2 stimulations per each level of unpleasantness and modality, i.e. 2 High disgust, 2 Low disgust, 2 High pain and 2 Low pain), in which participants received directly the olfactory or thermal stimulation without playing the game. The procedure for the "reference" trials was completely identical to that one for the "playing" trials, although it did not include the playing period.

Figure 3. Cyberball game task (Williams et al., 2000) – Picture seen on the screen with the ball moving. In the right side of the screen, participants could see player A or player C and in the left side of the screen, they could see player B or player D. In the middle bottom of the screen was represented participant's hand. The characters on the screen were moving as the ball to indicate whose turn it was to play.

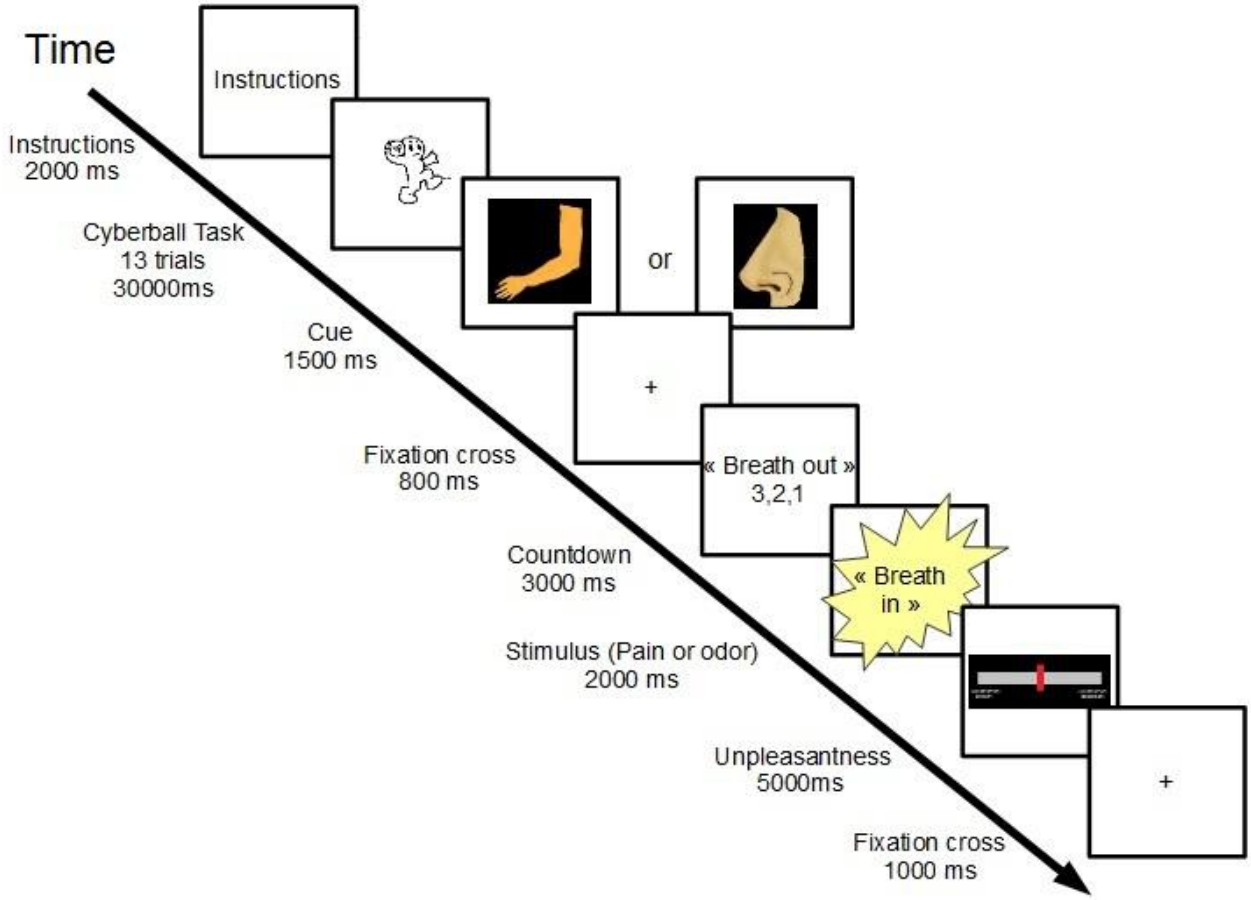

Figure 4. Procedure for playing sessions.

2.3.4 Questionnaires

Finally, to control which covariates might influence our dependent measure (ratings of unpleasantness), we asked participants to fill a battery of psychometric questionnaires at home, for half of them, and at the beginning and at the end of the experiment for the rest. Indeed, a number of studies have suggested that the existence of large interindividual differences in pain sensitivity may be due to psychological factors, such as anxiety, depression and negative affect. For instance, it has been shown that negative mood and anxiety increase the sensitivity to pain (Rhudy & Meagher, 2000; Starr, Houle, & Coghill, 2010). While Schienle et al. (2005) and Reuter et al. (2004) found a large effect of trait anxiety on the neural processing of disgust.

A few days before the experiment participants completed at home the State-Trait Anxiety Inventory (STAI Y-A&B; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983) to measure anxiety trait, the Beck Depression Index (BDI; Beck, & Beamesderfer, 1974; Collet, & Cottraux, 1985), the Social Anhedonia Scale (SAS; Chapman, Chapman, & Raulin, 1976), the Rejection Sensitivity Questionnaire (RSQ; Berenson et al., 2010) to measure the cognitive-affective processing disposition to anxiously expect rejection (rejection expectancy and rejection sensitivity), the Attachment Style Questionnaire (ASQ; Hazan and Shaver, 1987), the Pain Catastrophizing Scale (PCS; Sullivan, 1995)to measure the catastrophizing ideation when experiencing pain. Finally, they answered the Disgust Scale Revised (DS R1-2; Olatunji et al., 2007) to measure the sensitivity to disgust.

After the experiment, we checked if our exclusion manipulation worked by asking participants on a scale going from 1 (not at all) to 9 (completely) how much did they feel to belong to the two groups, A&B vs. C&D, (belongingness), how much did they think to be appreciated by two groups (self-value), how much did they feel to be included (inclusion) and excluded (exclusion) by the two groups, how much did they like the two groups (pleasantness) and how much did they think to be liked by them (self-pleasantness). Then, we measured their distress assessing their feelings of meaningfulness ("My life is meaningless) and control (I am in control of my life). Finally, participants were asked to write what was the goal of this experiment and how can we improve it according to them. It was a way to find out if participants realized what we were testing and if they understood that the others participants were confederates. If they did not feel excluded by the group C&D and understood what our manipulation was, we did not keep their data.

2.4 Data Processing

2.4.1 Online ratings

As first step, for each subject, we excluded those blocks in which the "reference" trials with (i) high pain or high disgust stimulations were rated as equally unpleasant or less unpleasant than the corresponding low pain and low disgust, (ii) high pain or high disgust stimuli were rated

as equal or less unpleasant that -1, and (iii) low pain or low disgust were rated as equal or more unpleasant than -4. As a result, 27 out of 60 blocks (2 blocks per participant*30 participants) collected in the whole study were removed from the final analysis, to insure that, for the rest of the data, high pain and high disgust stimulations were felt as more unpleasant that the corresponding conditions. Therefore, we had removed both blocks of 5 participants from statistical analyses, resulting in a total N of 25 subjects (16 women and 9 men; M = 21.12, SD = ± 2.2 y.o., range between 18 and 27 y.o.). Keep in mind that subjects/sessions were never excluded on the basis of the ratings in cyberball trials, which were the real aim of this study. On average, participants showed no pathological anxiety disorders (on STAI Y-A&B M = 40.88, SD = ± 9.57) or pathological depression disorders (on BDI M = 4.28, SD = ± 3.53).

Ratings of unpleasantness (from stimuli events) were analyzed through repeated measure ANOVA by crossing the factors *Unpleasantness* (high vs. low), *Modality* (pain vs. disgust) and *Social Play* (inclusion vs. exclusion) for the "playing" trials and by crossing only the factors *Unpleasantness* (high vs. low), and *Modality* (pain vs. disgust) for the "reference" trials. When significant interaction effects in the ANOVAs were identified, these were further explored via Bonferroni-corrected post-hoc t-tests.

Then, we decided to examine whether the effects of social play on the unpleasantness were influenced by the degree to which participants were affected by the manipulation. To do this, we correlated the differential values of self-reports of social distress (belongingness, self-value, pleasantness, self-pleasantness, and subjective inclusion/exclusion rating, described above) associated with players C&D (who excluded the participant) and A&B (who included the participants) and the differential unpleasantness ratings of high painful stimuli, when following exclusion blocks relative to inclusion.

Finally, we ran principal component analysis on all 6 self-reports to estimate an overall scalar measure of the task-effectiveness.

2.4.2 Physiological Measures

During the main experiment, we collected three types of physiological measures: electrodermal activity and finger pulse rate to indicate the autonomic arousal (indicator of automatic emotional reactions) and respiration to control if participants were correctly sniffing the odors. For these measures, we used the MP150 Biopac Systems (Santa Barbara, CA) with a 1000 Hz sampling rate.

To measure the electrodermal activity, Beckman Ag-Agcl electrodes (8mm 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 middle and the third fingers. For the analysis, a low pass filter of 1Hz and high pass filter of 0.005Hz was applied to filter the data.

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. A low pass filter of 30Hz and a high pass filter of 1Hz were used on the data which were also reduced to pulse rate in beats/minute (BPM).

Finally, the respiratory activity was measured thanks to a 2.5mm 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 odors. This one was connected to a differential pressure transducer (TSD160A; ± 2.5cm H_2O sensitivity range). It allowed to record continuously variations in the nostril airflow and to determine the inhalation and exhalation phases. A low pass filter of 10Hz was used.

Among the 25 participants selected for the behavioral analyses, the data of three participants for the electrodermal and respiratory activities and four participants for the heart rate could not be taken into account due to the high amount of artefacts or the bad quality of the signals. The data of these participants were therefore excluded from statistical analyses, resulting in a total N of 22 subjects for the electrodermal and respiratory activities and of 21 for the heart rate. In addition, due to technical problems during the acquisition of data of one subject, we missed his physiological data in low pain during the inclusion condition and low disgust in the exclusion condition. Therefore, in these conditions we could analyze the data of 21 participants for electrodermal activity and respiration and those of 20 subjects for Heart Rate

For each subject, the time course of each physiological measure was transformed into a z-score, down sampled to 10Hz, 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 model using finite impulse response (FIR) as basis function, which poses no a priori assumption on the properties of the event-related response. We synchronized all three physiological measures with the start of the countdown, after the cue presentation, and we modeled stimuli events with 20 bins of 1 second per bin, covering the 3000ms countdown, and the following time in which stimuli were delivered and rated.

As we did for the behavioral data, for the "playing" trials we analyzed data related to physiological parameter through a repeated measure ANOVA by crossing the factors *Unpleasantness* (high vs. low), *Time* (time bins – starting after the countdown, at the bin number 4) and *Social Play* (inclusion vs. exclusion) and for the "reference" trials by crossing only the factors *Unpleasantness* (high vs. low), and *Time* (time bins).

3 Results

3.1 Behavioral measures

3.1.1 Reference trials

To examine the effects of our olfactory and thermal stimulations on the unpleasantness, we entered the data related to the "reference" trials in a repeated-measure ANOVA crossing the factors *Unpleasantness* (high vs. low) and *Modality* (pain vs. disgust) (See Figure 5A). Consistently with our preselection approach (see above), results showed a main effect of Unpleasantness ($F(1,24) = 184.90$, $p < 0.001$), highlighting that High Disgust (HD) and High Pain (HP) were respectively more unpleasant than Low Disgust (LD) and Low Pain (LP). Furthermore, we found no effect of Modality or any interaction between both factors (p's > 0.300). This means that painful stimulations were not more or less unpleasant compared to disgusting stimulations, but they were comparably-unpleasant.

3.1.2 Playing trials

Next, to examine the effect of social exclusion on the unpleasantness, we entered the data related to "playing" trials in a repeated-measure ANOVA crossing the factors *Unpleasantness* (high vs. low), *Modality* (pain vs. disgust) and *Social Play* (inclusion vs. exclusion). As for the "reference" trials, we found a main effect of Unpleasantness ($F(1,24) = 121.20$, $p < 0.001$), indicating that our highly painful and disgusting stimulations were respectively more unpleasant than our low stimulations. Furthermore, there was a main effect of Modality ($F(1,24) = 4.62$, $p < 0.050$), reflecting that painful stimulations were more unpleasant than disgusting stimulations. A main effect of Social Play ($F(1,24) = 6.92$, $p < 0.050$) was also found, indicating that participants rated differently the unpleasantness of the stimulations after being excluded than after being included. However, we did not find any interaction between Unpleasantness and Modality neither between Social Play and Unpleasantness nor between Modality and Social Play (*p*'s > 0.300). Importantly, there was a significant triple interaction between all factors ($F(1,24) = 4.96$, $p < 0.050$). To better understand this triple interaction, we further computed 4 post-hoc Bonferroni-corrected t-tests, examining each of the four possible combinations of Social Play and stimulus Modality (critical *p*-value = 0.05/4 = 0.0125). We found a significant decrease of unpleasantness for pain when a highly thermal stimulation was preceded by the exclusion condition (relative to the inclusion condition) (HP_Exclusion < HP_Inclusion: $t(24) = -3.35$, $p < 0.0125$). More critically, the same decrease of unpleasantness was not observed when a low thermal nor high/low olfactory stimulation were preceded by the exclusion condition (p's > 0.064). These findings indicate that the social exclusion influenced only the degree of unpleasantness of high thermal stimulations. In other words, what it has been observed for high pain cannot be extended to another unpleasant modality, such as disgust. (See Figure 5B and 5C).

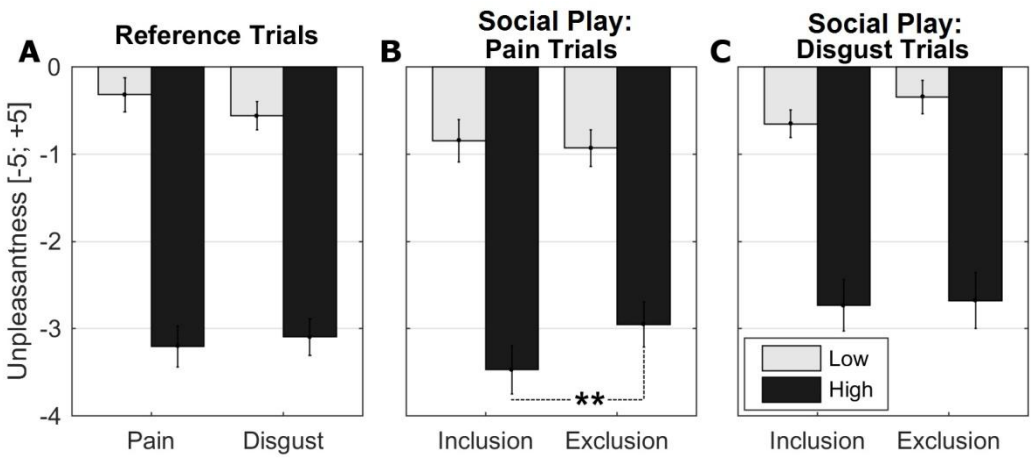

Figure 5. (A) Repeated-measure ANOVA crossing the factors *Unpleasantness* (high vs. low), *Modality* (pain vs. disgust) in the reference trials. (B) Repeated-measure ANOVA crossing the factors *Unpleasantness* (high vs. low) and *Social Play* (inclusion vs. exclusion) when participants received thermal stimulations during the playing trials. (C) Repeated-measure ANOVA crossing the factors *Unpleasantness* (high vs. low) and *Social Play* (inclusion vs. exclusion) when participants received olfactory stimulations during the playing trials.

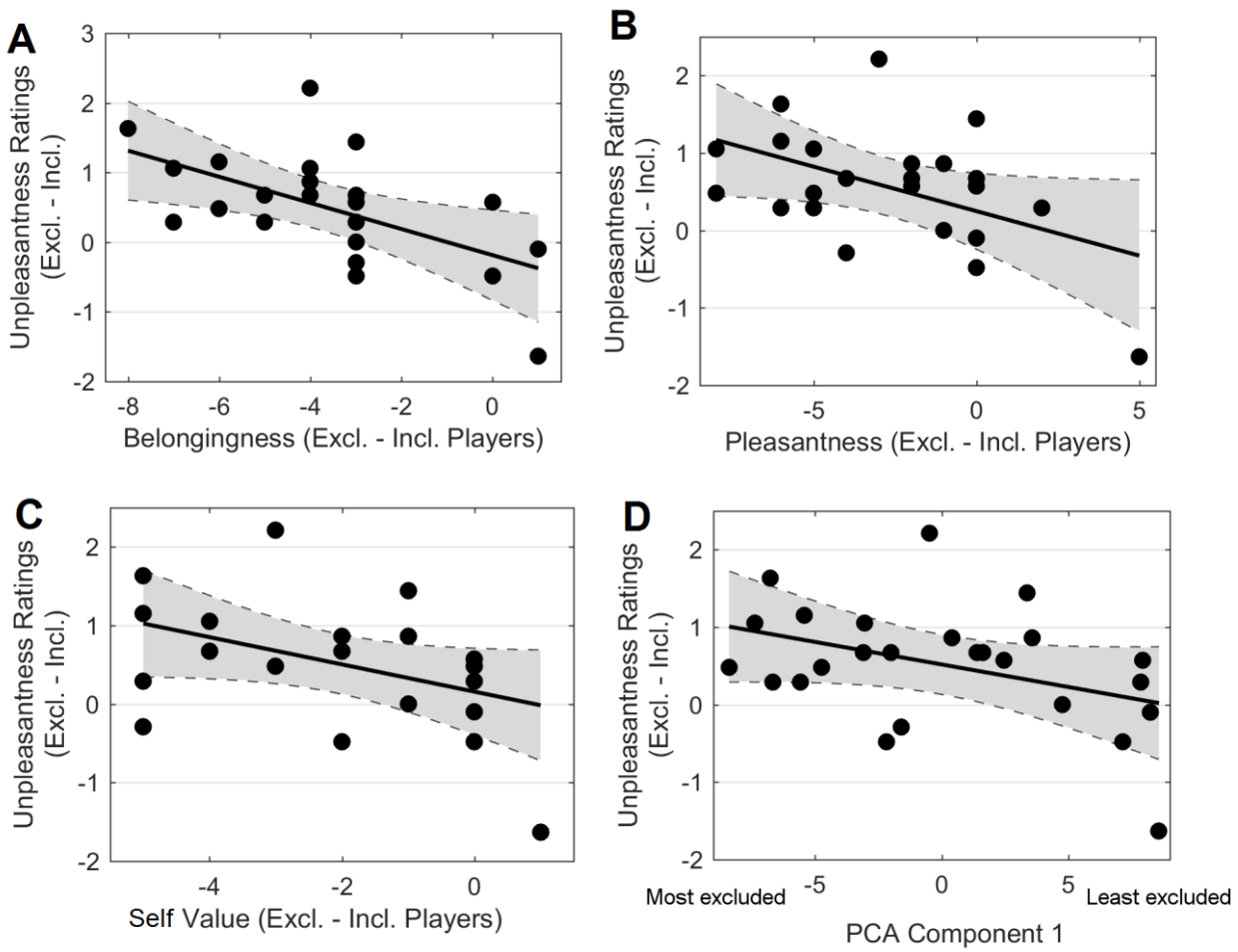

Figure 6. Pearson correlations between differential values of unpleasantness ratings of HP after exclusion relative to inclusion and differential values of self-reports of distress for players C&D relative to A&B. (A) Pearson correlation between the unpleasantness and the feeling of belongingness to the other players (B) Pearson correlation between the unpleasantness and the pleasantness for the other players (C) Pearson correlation between the unpleasantness and the self-value (D) Principal component analysis between the unpleasantness ratings and the feelings of exclusion.

Finally, we examined whether the effects observed above were influenced by the degree to 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), we took the differential values associated with players C&D (who excluded participants) and A&B (who included participants). Indeed, subjects mostly affected by the paradigm should have reported lower rates of belongingness/self-value/pleasantness/inclusion (and higher rates of exclusion) for players C&D relative to A&B, 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 differential unpleasantness ratings of high painful stimuli, when following exclusion blocks relative to inclusion. 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 $r = -0.58$, $p < 0.050$): individuals who felt to belong the least with C&D (relative to A&B) were those who rated post-exclusion high pain as far less unpleasant that post-inclusion high pain (See Figure 6A). 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 ($r \leq -0.44$, $p \leq 0.027$, Figure 6B and 6C – all other reports $|r| \leq 0.27$, $p \geq 0.050$). Furthermore, we ran a principal component analysis on all 6 self-reports to estimate an overall scalar measure of the task-effectiveness. Also the scores of the resulting principal component (coefficients: belongingness 0.39, self-value 0.25, inclusion 0.35, exclusion -0.43, pleasantness 0.54, self-pleasantness 0.42) were found to be correlated with subjects' ratings ($r = -0.41$, $p < 0.050$), confirming that the effect of social exclusion on pain unpleasantness was indeed stronger in those subjects who were mostly affected by the experimental manipulation (See Figure 6D). The ratings associated with low pain, or high/low disgust were never significantly correlated with post-experiment self-reports, neither at the most lenient α-errors ($|r| \leq 0.24$, $p \geq 0.05$).

3.2 Questionnaires

We investigated the potential influence that could have individual psychometric characteristics (like anxiety and depression, Social Anhedonia (SA), Rejection Sensitivity (RS), Attachment style (AS), Pain catastrophizing (PC) and Disgust Sensitivity (DS)) on the way participants evaluated as unpleasant highly painful stimulation. To do this, we correlated the scores of anxiety, depression, SA, RS, AS, PC and DS with the differential unpleasantness of

high painful stimulation when following exclusion blocks relative to inclusion blocks. No significant correlation was found (p's > 0.35).

3.3 Physiological measures

3.3.1 Electrodermal activity

3.3.1.1 Pain & disgust

3.3.1.1.1 Reference trials

First, we observed the effect of our thermal stimulation on electrodermal activity. For this, we entered our data related to the "reference" trials in a repeated-measure ANOVA crossing the factors *Unpleasantness* (high vs. low) and *Time* (time bins – starting after the countdown, at the bin number 4) separated per each modality (pain, disgust) (See Figure 7A and 7B). As expected, we found a main effect of Time with painful stimulation (F(16,336) = 2.54, p < 0.0001) and with disgusting stimulation (F(16,320) = 1.79, p < 0.050), highlighting that electrodermal activity was not the same across time and especially was different during and after the stimulation. Indeed, we could observe an increase of the skin conductance response (SCR) which was first lower and then more enhanced. No main effect of Unpleasantness with painful stimulation (p = 0.068) nor with disgusting stimulation (p = 0.383) was found. On the other hand, an effect of interaction between Unpleasantness and Time (F(16,336) = 4.19, p < 0.001) was obtained with painful stimulation but not with disgusting stimulation (p = 0.932). Based on this result, we ran post-hoc Bonferroni corrected 1-tailed t-tests, testing for increased SCR for high pain relative to low pain at each time bin (critical p-value = 0.05/17 = 0.0029). A significant difference has only been observed at the time bin 17 (HP > LP: t(21) = 3.07, p < 0.0029), time bin 18 (HP > LP: t(21) = 3.28, p < 0.0029) and time bin 19 (HP > LP: t(21) = 3.13, p < 0.0029). No other time bin was associated with a significant correlation, although at a more lenient p-value (0.05, uncorrected), significant results have been observed from time bin 12 to time bin 20 (p < 0.04). At the other time bins, no significant difference was found (p's > 0.13). Therefore, these findings revealed that the mean

level of the SCR was higher in the condition high pain stimulation compared to low pain stimulation only from 10 sec to 12 sec after the reception of the stimulation.

3.3.1.1.2 Playing trials

Then, we used our data related to the "playing" trials in a repeated-measure ANOVA crossing the factors *Unpleasantness* (high unpleasantness vs. low unpleasantness), *Social play* (Inclusion vs Exclusion) and *Time* (among the 20 bins), again separated per each modality (pain, disgust) (See Figure 7C, 7D, 7E & 7F). This analysis showed us, as for "reference" trials, a main effect of Time for pain stimulation ($F(16,320) = 7.04$, $p < 0.001$) but also for disgust stimulation ($F(16,320) = 5.04$, $p < 0.001$), which could be again explained by the fact that the SCR was not the same during and after the stimulation. In addition, we noticed a main effect of Social play with painful stimulation ($F(1,20) = 7.18$, $p < 0.050$) as with disgusting stimulation ($F(1,20) = 11.35$, $p < 0.050$), revealing that the SCR was higher following inclusion condition compared to exclusion condition independently of the level of the stimulation unpleasantness. No main effect of Unpleasantness was found for painful stimulation ($p = 0.056$) or for disgusting stimulation ($p = 0.071$).

For painful stimulation, an interaction between Unpleasantness and Time ($F(16,320) = 3.445$, $p < 0.001$) was observed. So, we computed 17 post-hoc Bonferroni corrected 1-tailed t-tests for each Social Play condition at every time bin to assess for stronger SCR in high vs. low painful stimulations (critical p-value = 0.05/17 = 0.0029). In the inclusion condition, a significant difference was found at the time bin 16 (HP > LP: $t(21) = 3.76$, $p < 0.001$), the time bin 17 (HP > LP: $t(21) = 3.55$, $p < 0.001$), the time bin 18 (HP > LP: $t(21) = 3.60$, $p < 0.001$), the time bin 19 (HP > LP: $t(21) = 3.68$, $p < 0.001$) and the time bin 20 (HP > LP: $t(21) = 3.64$, $p < 0.001$). No other significant result was found although at a more lenient p-value (0.05, uncorrected), significant results have been observed at the time bin 12 (HP > LP: $t(21) = 1.88$, $p < 0.050$), at the time bin 13 (HP > LP: $t_{(21)} = 2.34$, $p < 0.050$), at the time bin 14 (HP > LP: $t(21) = 2.41$, $p < 0.050$) and the time bin 15 (HP > LP: $t(21) = 2.97$, $p < 0.050$). At no other time bin a significant difference was obtained with or without correction (p's > 0.224). These findings suggested that in inclusion sessions, the mean level of the SCR was higher after a high painful stimulation relative

to low painful stimulation 10 sec after the reception of the stimulation. While in exclusion sessions, no significant difference has been found with Bonferroni correction but with an uncorrected p-value (0.05, uncorrected) we can observe a significant difference at the time bin 16 (HP > LP: $t(20) = 1.91$, $p < 0.050$), the time bin 17 (HP > LP: $t(20) = 2.20$, $p < 0.050$), the time bin 18 (HP > LP: $t(20) = 2.53$, $p < 0.050$), the time bin 19 (HP > LP: $t(20) = 2.45$, $p < 0.050$) and the time bin 20 (HP > LP: $t(20) = 2.08$, $p < 0.050$). The other differences were not significant (p's > 0.07). This interaction between Unpleasantness and Time was not found with disgusting stimulation ($p = 0.893$), whereas an interaction between Social Play and Unpleasantness ($p = 0.001$) has been observed, indicating that the difference of mean between the SCR after high and low disgusting stimulations were not the same in inclusion condition compared to the exclusion condition. Again, 17 post-hoc Bonferroni corrected 1-tailed t-tests have been computed at each time bin to assess for stronger SCR in high vs. low disgusting stimulations (critical p-value = 0.05/17 = 0.0029). No significant value were found with Bonferroni correction in inclusion and exclusion condition but with an uncorrected p-value (0.05, uncorrected), we can observed a difference in inclusion condition at the time bin 18 (HD > LD: $t(21) = 2.33$, $p < 0.050$), at the time bin 19 (HD > LD: $t(21) = 2.60$, $p < 0.050$) and at the time bin 20 (HD > LD: $t(21) = 2.21$, $p < 0.050$). In exclusion condition, we also noticed a difference at the time bin 9 (HD > LD: $t(21) = 1.92$, $p < 0.050$). No other significant difference was found (p's > 0.061). No another effect of interaction was found (p's > 0.060) with painful and disgusting stimulation.

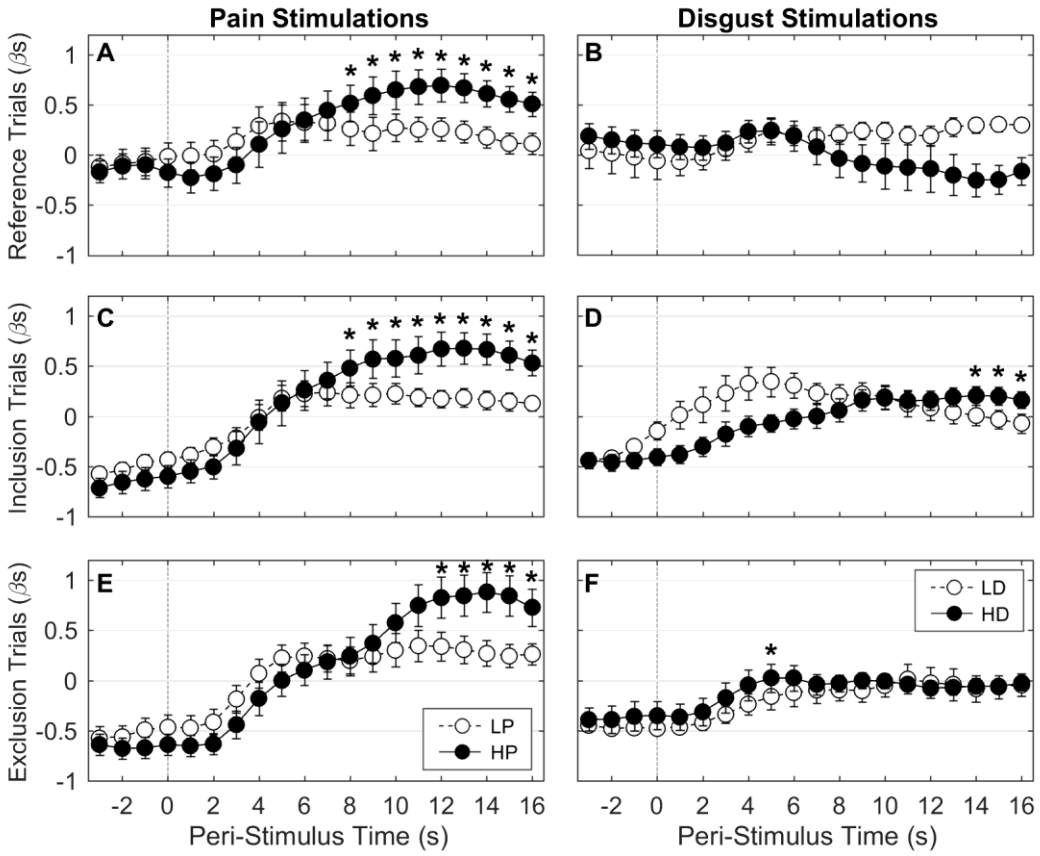

Figure 7. SCR's mean across time. 0 sec indicates the onset of the stimulation for disgusting stimulation whereas the painful stimulation started to be felt at 2 sec. (A) SCR's mean (βs) during reference trials with a high or low painful stimulation. (B) SCR's mean (βs) during reference trials with a high or low disgusting stimulation. (C) SCR's mean (βs) during Inclusion trials with a high or low painful stimulation. (D) SCR's mean (βs) during Inclusion trials with a high or low disgusting stimulation. (E)SCR's mean (βs) during Exclusion trials with a high or low painful stimulation. (F) SCR's mean (βs) during Exclusion trials with a high or low disgusting stimulation.

3.3.2 Heart rate

3.3.2.1 Pain & disgust

3.3.2.1.1 Reference trials

Second, we were interested in the effect of our thermal stimulation on the heart rate (HR) across time. Data related to the "reference" trials were entered in a repeated-measure ANOVA crossing the factors *Unpleasantness* and *Time* (See Figure 8A & 8B). As before, a main effect of Time was found with painful stimulation ($F(16,320) = 2.90$, $p < 0.001$) and with disgusting stimulation ($F(16,304) = 3.45$, $p < 0.001$), meaning that the HR was not similar during and after the stimulation. In fact, when we observed in the graphics and especially the one related to disgusting stimulation (Figure 8A & 8B) an increase of activation at 0sec and then a decrease, which can be related respectively to the inspiration and the expiration of the participant. No main effect of unpleasantness was observed with painful ($p = 0.486$) and disgusting stimulation ($p = 0.733$). An effect of interaction between Unpleasantness and Time ($F(16,320) = 2.40$, $p < 0.050$) was obtained with the painful stimulation. This indicates that participant's differential (high vs. low pain) HR values changed across time. No interaction was found for the case of disgust ($p = 0.493$). To go further, we computed 17 Bonferroni post-hoc 1-tailed t-tests on each time bin to probe for accelerated cardiac responses for high vs. low pain. No significant effect under Bonferroni threshold was found with the correction, but at a more lenient p-value (0.05, uncorrected) a significant difference was found at the time bin 12 (HP > LP: $t(20) = 2.08$, $p < 0.050$), time bin 13 (HP > LP: $t(20) = 2.14$, $p < 0.050$) and the time bin 20 (HP > LP: $t(20) = 2.03$, $p < 0.050$).

3.3.2.1.2 Playing trials

Again, a second repeated-measure ANOVA crossing factors *Time*, *Unpleasantness* and *Social play* have been done with the "playing" trials (See Figure 8C, 8E, 8F & 8D). A main effect of Time with painful stimulation ($F(16,304) = 4.01$, $p < 0.001$) and disgusting stimulation

($F(16,304) = 6.93$, $p < 0.001$) has again been found. No main effect of Unpleasantness ($p = 0.200$) nor Social pain ($p = 0.441$) has been found for painful stimulations nor a main effect of Unpleasantness ($p = 0.960$) nor a main effect of Social play ($p = 0.390$) for disgusting stimulations. An interaction between Social play and Unpleasantness has also been obtained with painful ($F(1,19) = 16.16$, $p < 0.001$) and disgusting stimulation ($F(1,19) = 5.75$, $p < 0.050$), reflecting that the mean of the HR was higher in inclusion compared to exclusion and even more when it was a high painful stimulation compared to a low painful stimulation, whereas with disgusting odors it was the exclusion condition which was higher than the inclusion condition and even bigger when it was a high disgusting odor compared to a low disgusting odor. To have a better understanding, we realized for each type of stimulation 17 Bonferroni post-hoc 1-tailed t-tests (critical p-value = 0.05/17 = 0.0029) on each bin to probe evaluate the difference cardiac responses for high vs. low pain and for high vs. low disgust. For painful stimulation, we found a significant difference at the time bin 13 (HP > LP: $t(20) = 3.14$, $p < 0.0029$), at the time bin 17 (HP > LP: $t(20) = 3.22$, $p < 0.002$) , at the time bin 19 (HP > LP: $t(20) =3.73$, $p < 0.001$) and at the time bin 20 (HP > LP: $t(20) = 3.59$, $p < 0.001$). Without the Bonferroni correction (0.05, uncorrected), we found a significant difference at the time bin 5 (HP > LP: $t(20) = 1.87$, $p <0.050$), at the time bin 10 (HP > LP: $t(20) = 1.88$, $p < 0.050$), at the time bin 11 (HP > LP: $t(20) = 2. 31$, $p < 0.050$), at the time bin 12 (HP > LP: $t(20) = 2.94$, $p < 0.050$), at the time bin 14 (HP > LP: $t(20) = 2.94$, $p < 0.050$), at the time bin 15 (HP > LP: $t(20) = 1.80$, $p < 0.050$), at the time bin 16 (HP > LP: $t(20) = 2.22$, $p < 0.050$) and at the time bin 18 (HP > LP: $t(20) = 2.22$, $p < 0.050$). No significant effect with or without Bonferroni correction was found in exclusion condition for painful stimulation (p's >0.18). For disgusting stimulation, no significant difference was found in the t-tests (p's > 0.05). No other interaction between factors was found (p's > 0.097).

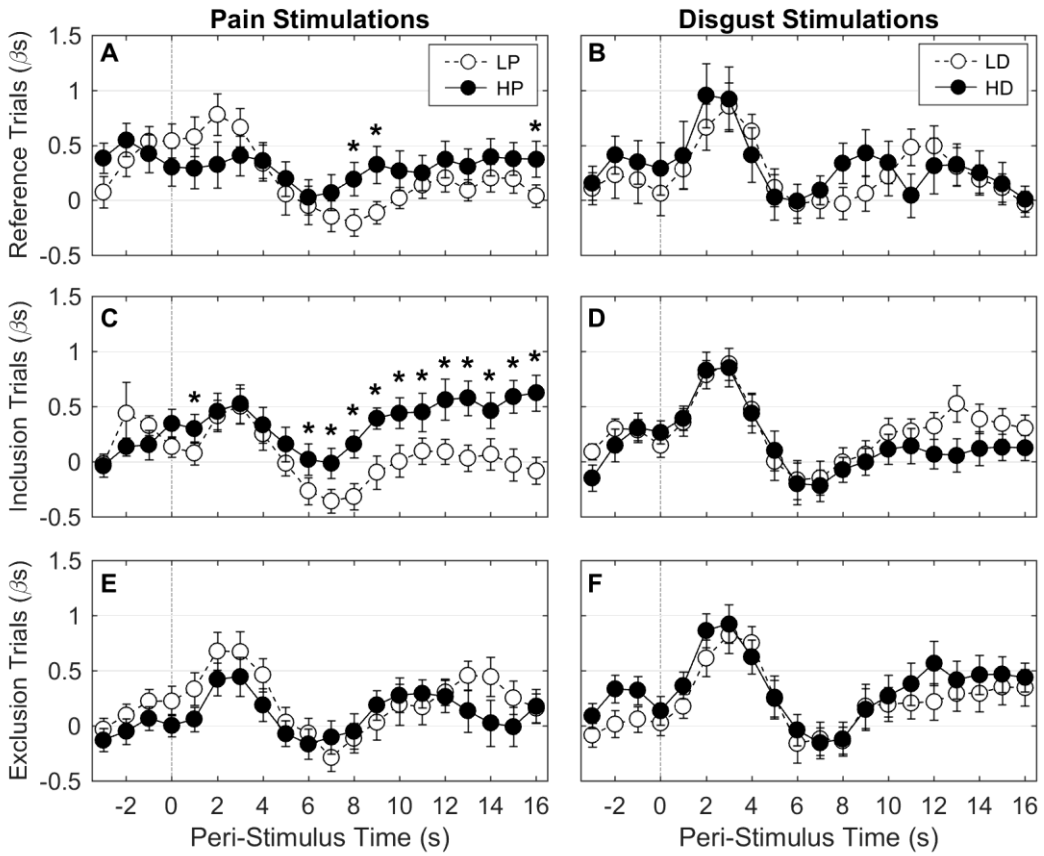

Figure 8. HR's mean across the time. 0 sec indicates the onset of the stimulation for disgusting stimulation whereas the painful stimulation started to be felt at 2sec. (A) HR's mean (βs) during reference trials with a high or low painful stimulation. (B) HR's mean (βs) during reference trials with a high or low disgusting stimulation. (C) HR's mean (βs) during Inclusion trials with a high or low painful stimulation. (D) HR's mean (βs) during Inclusion trials with a high or low disgusting stimulation. (E) HR's mean (βs) during Exclusion trials with a high or low painful stimulation. (F) HR's mean (βs) during Exclusion trials with a high or low disgusting stimulation.

3.3.3 Respiration

3.3.3.1 Pain & disgust

3.3.3.1.1 Reference trials

Third, we looked at the effect of painful stimulation on respiration (inspiration air volume) across time. Data related to the "reference" trials were entered in a repeated-measure ANOVA crossing the factors *Unpleasantness* and *Time* (See Figure 9A & 9B). Again as expected, a main effect of Time has been observed with painful ($F(16,336) = 4.99$, $p < 0.001$) and disgusting stimulation ($F(16,320) = 6.51$, $p < 0.001$), indicating that the mean of respiration was not the same during and after the stimulation. As described in the graphics (Figure 9A & 9B), close to 0sec, there was a decrease of the respiration level, suggesting the expiration and then the inspiration of the participant related to the instructions visible on the screen. However, we found no main effect of Unpleasantness with painful ($p = 0.516$) or disgusting stimulation ($p = 0.416$) nor interaction between Unpleasantness and Time with painful ($p = 0.371$) and disgusting stimulation ($p = 0.703$).

3.3.3.1.2 Playing trials

Finally, another repeated-measure ANOVA crossing factors *Time*, *Unpleasantness* and *Social play* has been done with the date related to the "playing" trials (See Figure 9C, 9D, 9E & 9F). Again a main effect of Time has been found with painful ($F(16,320) = 7.77$, $p < 0.001$) and disgusting stimulation ($F(16,320) = 9.14$, $p < 0.001$).

With painful stimulation a main effect of unpleasantness ($F(1,20) = 18.77$, $p < 0.001$) has been observed. This means that the level of respiration was higher for high painful stimulation compared to low painful stimulation. No main effect of Social play ($p = 0.124$) was found nor an interaction between Social play and Unpleasantness ($p = 0.743$) nor an interaction between Social play and Time ($p = 0.743$). But an interaction between Unpleasantness and Time ($F(16,320) = 1.95$, $p < 0.050$) as a three-way interaction ($F(16, 320) = 1.88$, $p < 0.050$) have been obtained,

showing that the respiration was changing across time and even more if it was after a low painful stimulation compared to a high painful stimulation. To understand what was happening, we computed 17 post-hoc Bonferroni corrected t-test (critical p-value = 0.05/17 = 0.0029) in each Social play condition at every time bin, comparing the mean level of respiration after a high or a low painful stimulation. No significant difference was found in the inclusion condition with Bonferroni correction although, with a more lenient p-value (0.05, uncorrected), a significant difference is visible at the time bin 11 (HP < LP: $t(21) = -1.85$, $p < 0.050$), the time bin 15 (HP < LP: $t(21) = -2.34$, $p < 0.050$), the time bin 17 (HP < LP: $t(21) = -2.94$, $p < 0.050$), the time bin 18 (HP < LP: $t(21) = -2.27$, $p < 0.050$) and the time bin 19 (HP < LP: $t(21) = -2.45$, $p < 0.050$). Only one significant difference was found in exclusion condition at the time bin 18 (HP < LP: $t(20) = -3.56$, $p < 0.001$) and also only one significant difference was found without Bonferroni correction (0.05, uncorrected p-value) at the time bin 13 (HP < LP: $t(20) = -2.37$, $p < 0.050$). According to the graphic (see Figure 9C & 9E), we can see that the level of respiration is higher after receiving a low painful stimulation compared to a high disgusting stimulation on those different times. No other significant difference was found in the exclusion condition (p's > 0.070).

With disgusting stimulation, no main effect of Social play ($p = 0.104$) and no main effect of Unpleasantness ($p = 0.371$) was found. However, a significant interaction between Social play and Time ($F(16,320) = 2.70$; $p < 0.001$) has been noticed, showing that the mean level of respiration was higher in inclusion condition compared to exclusion condition and even more depending on the time bin. We investigated this difference of respiration between exclusion and inclusion condition across the time by doing 17 post-hoc Bonferroni corrected 1-tailed t-test (critical p-value = 0.05/17 = 0.0029). We did not observe any significant difference at each time bin under the Bonferroni threshold. But with a more lenient p-value (0.05, uncorrected), we found significant differences at the time bin 13 (ED < ID: $t(21) = -1.73$, $p < 0.050$), at the time bin 14 (ED < ID: $t(21) = 1.90$, $p < 0.050$), at the time bin 16 (ED < ID: $t(21) = -2.24$, $p < 0.050$) and at the time bin 17 (ED < ID: $t(21) = -2.34$, $p < 0.050$). No other interaction between factors was obtained (p's > 0.383).

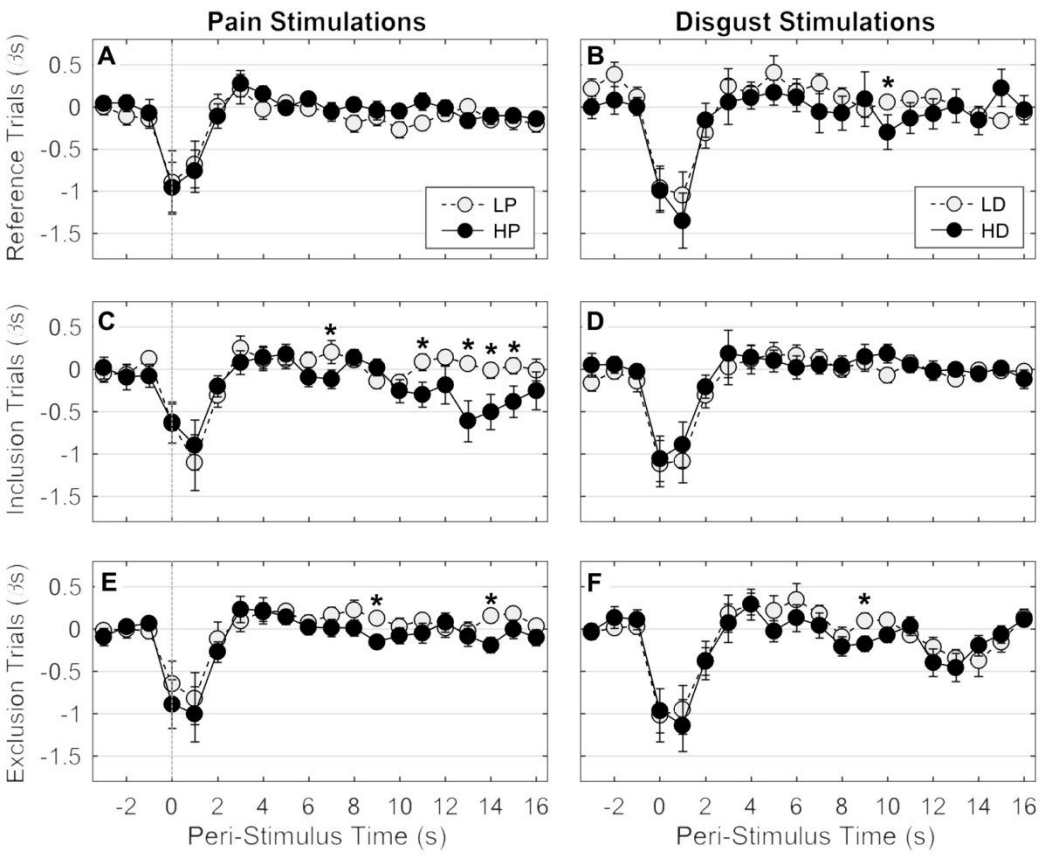

Figure 9. Respiration level's mean across the time. 0 sec indicates the onset of the stimulation for disgusting stimulation whereas the painful stimulation started to be felt at 2 sec. (A) Respiration level's mean (βs) during reference trials with a high or low painful stimulation. (B) Respiration level's mean (βs) during reference trials with a high or low disgusting stimulation. (C) Respiration level's mean (βs) during Inclusion trials with a high or low painful stimulation. (D) Respiration level's mean (βs) during Inclusion trials with a high or low disgusting stimulation. (E) Respiration level's mean (βs) during Exclusion trials with a high or low painful stimulation. (F) Respiration level's mean (βs) during Exclusion trials with a high or low disgusting stimulation.

4 Discussion

We exposed participants to painful and disgusting stimuli after they played a virtual ball toss (cyberball) game in which they experienced social exclusion. We found that social exclusion (compared to an inclusion control condition) led to less unpleasant ratings for painful stimuli, but not for comparably-unpleasant disgust. This effect was stronger in those participants who were more affected by the manipulation, as measured by post-experimental debrief questionnaires. Finally, we discovered that social exclusion had an impact also on autonomic response to pain as measured by skin conductance response (SCR) but also on heart rate (HR). Overall, our data indicated that social exclusion has an influence on pain sensitivity but not on the sensitivity of other comparably-unpleasant stimuli. As consequence, the link between social exclusion and physical pain highlighted in the previous studies could not be considered as reflective of supramodal dimensions such as unpleasantness, but rather could reflect sensory-specific components of the painful experience.

A popular view in the literature considers that social and physical pain are underpinned by shared representational code because they are activating the same neuronal region (dACC and AI), and because they influence one another. However, scholars have recently criticized this idea on two independent grounds. On the one side, it has been argued that overlapping activation maps do not necessarily imply shared representational level; consistently, Woo et al. (2014) recently pointed that the activity patterns evoked by physical and social pain were, certainly overlapping in key brain regions, but ultimately independent. Thus, social exclusion should not be considered "painful", but an independent experience with its own idiosyncratic properties. On the other hand, it has been suggested that neuroimaging and behavioural effects linking physical pain to social exclusion could be confounded by some supramodal dimensions related to unpleasantness, arousal or salience (Iannetti et al., 2013). Thus, social exclusion should not be considered "painful", but simply "unpleasant".

The results from this study cut at the core of this debate. Because unpleasantness was carefully matched between disgust and physical pain, it provided a unique opportunity to assess whether social exclusion would have influenced the subjective experience of both kinds of

somatic experiences equally, or of pain specifically. We found that the latter case was true, thus ruling out a role of supramodal dimensions and, in line with Eisenberger et al. (2003), MacDonald & Leary (2005) and the Social Pain theory, supporting a link between social exclusion and sensory-specific component of the painful experience. Thus, our results confirm that social exclusion is not "unpleasant", but it is specifically "painful".

These results were also reinforced by the analysis of physiological measures. SCR (see Figure 7) showed robust pain-related response following both reference trials (in which the stimulation was delivered in absence of the cyberball game) and inclusion trials. However, SCR was far less strong in trials in which participants felt excluded. Assuming that SCR is correlated with the level of arousal (Delplanque et al., 2009), we can interpret these results in terms social exclusion exerting an inhibitory effect on pain-related arousal. Similar effects were observed also for the analysis of cardiac response. Given that participants were engaged in a paradigm in which the respiration in the peri-stimulus time was constrained (through « Breath in » vs « Breath out » - see Figure 9), we had to disentangle the modulations of cardiac responses which were induced by the stimuli from those induced by the respiration. Following previous studies using the same paradigm (Delplanque et al., 2009; Sharvit et al., 2015), we consider respiration-evoked response a rapid increase and subsequent decrease in hearth rate within the first ~5 seconds of the stimulus onset (see Figure 8). Most importantly, what interests us is the modulation happening after the 5th, as it has been highlighted that stimulation would create an acceleration in this time-window correlated to its level of unpleasantness (Delplanque et al., 2009; Sharvit et al., 2015). This reaction has been explained as a defensive reaction to provide the ability to avoid the unpleasant stimulation (Turpin, Schaefer, & Boucsein, 1999; Vila et al., 2007). Consistently with that found in the analysis of SCR, also the analysis of cardiac response in the time-window of interest showed higher HR for painful (as opposed painless) thermal stimuli in both reference and inclusion trials. This difference almost disappeared in exclusion condition. This might suggest that highly painful stimulations were implicitly judged less unpleasant after social exclusion. The effect of HR could partially be confounded by the respiration pattern, as participants showed pain-related inspiration during the inclusion (but not exclusion) trials ~10 seconds after the stimulus onset.

Importantly, our results showed that social exclusion created an *analgesic* effect characterized by a decrease of the arousal and unpleasantness evoked by pain. This effect has also been found by Dewall et al. (2006) who explained this as a natural answer from the body when the amount of pain is too strong. Indeed, social pain cumulated with physical pain would provide a high level of distress paralyzing the body. At a certain point, when the pain is excessively strong to be endured, the brain would produce an analgesic effect which could decrease the distress to enable the body to potentially cope the pain and its origin. However, while in their experiment Dewall et al. (2006) found analgesic effects after using a task different from ours (participants received negative feedback about their future relationships after having filled a personality test), Eisenberger et al. (2006), who used the same Cyberball game as we did, discovered the opposite effect. In particular, Eisenberger et al. (2006) did not find a difference in thermal pain unpleasantness between different levels of exclusion, but found a positive correlation between exclusion-elicited distress and pain unpleasantness rating. This correlation was observed only after the exclusion condition, but not after the inclusion condition. According to Eisenberger et al. (2006), their results indicated that social exclusion would add to the pain signal, and leading to hypersensitivity. The divergence between the results of Dewall et al. (2006) and those of Eisenberger et al. (2006) was explained by Bernstein and Claypool (2012) as a consequence of different strengths of social exclusion. Normally, social exclusion signals would add to those elicited by physical pain, enhancing the pain sensitivity (as in Eisenberger et al. (2006)). However, if the social exclusion is too strong, as in Dewall et al. (2006) task, its summation with pain signal would elicit a tolerance threshold, and analgesia should be observed. Our data would fit this model only under the assumption that our Cyberball task would have elicited stronger exclusion than that of Eisenberger et al. (2006). Few considerations support this assumption. First, our study was organized as a complete within-subjects experiment, in which participants felt both excluded and included. Instead, in Eisenberger et al. (2006) the conditions were modelled between-subjects, with participants being assigned only to one condition of the Cyberball game (inclusion or exclusion). The between-subjects design has maybe weakened the social exclusion induction, as participants had no "inclusion" experience for comparison. Second, in our study the control condition was more inclusive than in Eisenberger et al. (2006) (participants received the ball ~40% of times), thus heightening the discrepancy with the

exclusion condition. In light of these considerations, we believe that the direction of our results are consistent with that predicted by the literature.

Differently from the case of pain, and from a previous study using similar setting (Sharvit et al., 2015), disgust had only minimal changes in physiological activity. No disgust-related modulation of SCR and HR was observed in the reference and inclusion trials. Paradoxically, weak (and yet measurable) responses were observed during the exclusion trials. While these data confirm also at the physiological level that pain and disgust were differentially affected by social exclusion, one might wonder why our odors did not elicit the same physiological response observed before (Sharvit et al., 2015). The main difference between the present and previous studies relies on the fact that here cues were only informative of the modality, but not of the unpleasantness, of the upcoming stimulus. Hence, differently from Sharvit et al. (2015), participants did not know whether the cued odorant would have been disgusting or not, thus insuring that effects related to unpleasantness were purely bottom-up. Although rating data clearly show that participants discriminated between the disgusting and neutral odors (with unpleasantness levels comparable to those of thermal stimuli), it is possible that the bottom-up information within the stimuli was not sufficiently strong to elicit a disgust-related physiological response. Participants might have become aware of the disgusting nature of the stimuli only later in the trial, when explicitly asked to provide a rating.

Furthermore, this study was run under the assumption that after a painful stimulation people will feel pain and after a disgusting stimulation they will feel disgust. Unfortunately, as we could not test emotional state after each trial, it is possible that another unpleasant emotional state could have been induced after pain stimulation as anger or fear. This might have partially confounded our effects (as well as the effects in previous studies using pain). Moreover, although we did our best to avoid odor contamination in between trials, some participants pointed out to us that they could sometimes smell residuals of the previous olfactory stimuli in the tube. This olfactory contamination might have weakened the strength of modality-specific effects, specifically in the case of disgust. In order to reinforce our results, it should be interesting to reproduce this experiment by using another kind of disgust induction as for example the absorption of a bitter beverage, as it was done in previous experiments (Eskine, Kacinik, & Prinz, 2011).

However, these limitations do not undermine the main message of this research, that social pain could influence physical pain but not comparably-unpleasant disgust. The most suitable interpretation of these data is that social exclusion would recruit a sensory-specific properties of the painful experience, but not supramodal properties of unpleasantness which are common to other aversive experiences as disgust.

5 Bibliography

Apkarian, A. V., Bushnell, M. C., Treede, R. D., & Zubieta, J. K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *European Journal of Pain*, *9*(4), 463–484. https://doi.org/10.1016/j.ejpain.2004.11.001

Bach, D. R., & Friston, K. J. (2013). Model-based analysis of skin conductance responses: Towards causal models in psychophysiology. *Psychophysiology*, *50*(1), 15–22. https://doi.org/10.1111/j.1469-8986.2012.01483.x

Benuzzi, F., Lui, F., Duzzi, D., Nichelli, P. F., & Porro, C. A. (2008). Does it look painful or disgusting? Ask your parietal and cingulate cortex. *Journal of Neuroscience*, *28*(4), 923–931. https://doi.org/10.1523/JNEUROSCI.4012-07.2008

Berenson, K. R., Gyurak, A., Downey, G., Garner, M. J., Mogg, K., Bradley, B. P., & Pine, D. S. (2010). Rejection sensitivity and disruption of attention by social threat cues, *43*(6), 1064–1072. https://doi.org/10.1016/j.jrp.2009.07.007.Rejection

Bernstein, M. J., & Claypool, H. M. (2012). Social exclusion and pain sensitivity: Why exclusion sometimes hurts and sometimes numbs. Personality and Social Psychology Bulletin, 38(2), 185-196.

Bowlby, J. (1973). *Attachment and loss (Vol. 2)* (Basic Book). New York.

Brewer, E. W., & Shapard, L. (2004). Employee Burnout: A Meta-Analysis of the Relationship Between Age or Years of Experience. *Human Resource Development Review*, *3*(2), 102–123. https://doi.org/10.1177/1534484304263335

Carden, S. E., Hernandez, N., & Hofer, M. A. (1996). The isolation and companion comfort responses of 7- and 3-day-old rat pups are modulated by drugs active at the opioid receptor. *Behavioral Neuroscience*, *110*(2), 324–30. https://doi.org/10.1037/0735-7044.110.2.324

Carden, S. E., & Hofer, M. A. (1990). Socially mediated reduction of isolation distress in rat pups is blocked by naltrexone but not by Ro 15-1788. *Behavioral Neuroscience*, *104*(3), 457–63. https://doi.org/10.1037/0735-7044.104.3.457

Chrea, C., Valentin, D., & Abdié, H. (2009). Graded structure in odour categories: A cross-cultural case study. *Perception, 38*(2), 292–309. https://doi.org/10.1068/p5687

Corradi-Dell'Acqua, C., Tusche, A., Vuilleumier, P., & Singer, T. (2016). Cross-modal representations of first-hand and vicarious pain, disgust and fairness in insular and cingulate cortex. *Nature Communications, 7*, 10904. https://doi.org/10.1038/ncomms10904

Delplanque, S., Grandjean, D., Chrea, C., Aymard, L., Cayeux, I., Le Calvé, B., … Sander, D. (2008). Emotional processing of odors: Evidence for a nonlinear relation between pleasantness and familiarity evaluations. *Chemical Senses*, *33*(5), 469–479. https://doi.org/10.1093/chemse/bjn014

Delplanque, S., Grandjean, D., Chrea, C., Coppin, G., Aymard, L., Cayeux, I., … Scherer, K. R. (2009). Sequential unfolding of novelty and pleasantness appraisals of odors: evidence from facial electromyography and autonomic reactions. *Emotion*, *9*(3), 316–328. https://doi.org/10.1037/a0015369

DeWall, C. N., & Baumeister, R. F. (2006). Alone but feeling no pain: effects of social exclusion on physical pain tolerance and pain threshold, affective forecasting, and interpersonal empathy. *Journal of Personality and Social Psychology, 91*(1), 1–15.

Eisenberger, N. I. (2003). Does Rejection Hurt? An fMRI Study of Social Exclusion. *Text, 290*(2003), 290–292. https://doi.org/10.1126/science.1089134

Eisenberger, N. I. (2012). The pain of social disconnection: examining the shared neural underpinnings of physical and social pain. *Nature Reviews. Neuroscience*, *13*(6), 421–34. https://doi.org/10.1038/nrn3231

Eisenberger, N. I. (2015). Social Pain and the Brain: Controversies, Questions, and Where to Go from Here. *Annual Review of Psychology, 66*(1), 601–629. https://doi.org/10.1146/annurev-psych-010213-115146

Eisenberger, N. I., & Lieberman, M. D. (2004). Why rejection hurts: A common neural alarm system for physical and social pain. *Trends in Cognitive Sciences*, *8*(7), 294–300. https://doi.org/10.1016/j.tics.2004.05.010

Eskine, K. J., Kacinik, N. A., & Prinz, J. J. (2011). A Bad Taste in the Mouth: Gustatory Disgust Influences Moral Judgment. *Psychological Science*, *22*(3), 295–299. https://doi.org/10.1177/0956797611398497

Ferdenzi, C., Roberts, S. C., Schirmer, A., Delplanque, S., Cekic, S., Porcherot, C., … Grandjean, D. (2013). Variability of affective responses to odors: Culture, gender, and olfactory knowledge. *Chemical Senses*, *38*(2), 175–186. https://doi.org/10.1093/chemse/bjs083

Gonsalkorale, K., & Williams, K. D. (2007). The KKK won't let me play: Ostracism even by a despised outgroup hurts. *European Journal of Social Psychology Eur.*, *37*(September 2006), 1176–1186. https://doi.org/10.1002/ejsp

Iannetti, G. D., & Mouraux, A. (2010). From the neuromatrix to the pain matrix (and back). *Experimental Brain Research*, *205*(1), 1–12. https://doi.org/10.1007/s00221-010-2340-1

Iannetti, G. D., Salomons, T. V., Moayedi, M., Mouraux, A., & Davis, K. D. (2013). Beyond metaphor: Contrasting mechanisms of social and physical pain. *Trends in Cognitive Sciences*, *17*(8), 371–378. https://doi.org/10.1016/j.tics.2013.06.002

Ischer, M., Baron, N., Mermoud, C., Cayeux, I., Porcherot, C., Sander, D., & Delplanque, S. (2014). How incorporation of scents could enhance immersive virtual experiences. *Frontiers in Psychology*, *5*, 1–11. https://doi.org/10.3389/fpsyg.2014.00736

Kalin, N. H., Shelton, S. E., & Barksdale, C. M. (1988). Opiate modulation of separation-induced distress in non-human primates. *Brain Research*, *440*(2), 285–292. https://doi.org/10.1016/0006-8993(88)90997-3

Kehoe, P., & Blass, E. M. (1986). Behaviorally functional opioid systems in infant rats: II. Evidence for pharmacological, physiological, and psychological mediation of pain and stress. *Behavioral Neuroscience*, *100*(5), 624–30. https://doi.org/10.1037/0735-7044.100.5.624

Kehoe, P., & Blass, E. M. (1986). Opioid-mediation of separation distress in 10-day-old rats: Reversal of stress with maternal stimuli. *Developmental Psychobiology*, *19*(4), 385–398. https://doi.org/10.1002/dev.420190410

Kehoe, P., & Boylan, C. B. (1994). Behavioral effects of kappa-opioid-receptor stimulation on neonatal rats. *Behavioral Neuroscience*, *108*(2), 418–23. https://doi.org/10.1037//0735-7044.108.2.418

Koban, L., Kross, E., Woo, C.-W., Ruzic, L., & Wager, T. D. (2017). Frontal-Brainstem Pathways Mediating Placebo Effects on Social Rejection. *The Journal of Neuroscience* (Vol. 37). https://doi.org/10.1523/JNEUROSCI.2658-16.2017

Konecka, A. M., & Sroczynska, I. (1990). Stressors and pain sensitivity in CFW mice. Role of opioid peptides. *Archives Of Physiology And Biochemistry*, *98*(2), 245–252. https://doi.org/10.3109/13813459009113984

Kross, E., Berman, M. G., Mischel, W., Smith, E. E., & Wager, T. D. (2011). Reply to Iannetti and Mouraux: What functional MRI responses to physical pain tell us about why social rejection "hurts." *Proceedings of the National Academy of Sciences*, *108*(30), E344–E344. https://doi.org/10.1073/pnas.1107241108

Kross, E., Berman, M. G., Mischel, W., Smith, E. E., & Wager, T. D. (2011). Social rejection shares somatosensory representations with physical pain. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(15), 6270–6275. https://doi.org/10.1073/pnas.1102693108

Kross, E., Egner, T., Ochsner, K., Hirsch, J., & Downey, G. (2007). Neural dynamics of rejection sensitivity. *Journal of Cognitive Neuroscience*, *19*(6), 945–56. https://doi.org/10.1162/jocn.2007.19.6.945

Kunz, M., Peter, J., Huster, S., & Lautenbacher, S. (2013). Pain and disgust: The facial signaling of two aversive bodily experiences. *PLoS ONE*, *8*(12), 1–11. https://doi.org/10.1371/journal.pone.0083277

Macdonald, G., & Leary, M. R. (2005). Why does social exclusion hurt? The relationship between social and physical pain. *Psychol Bull*, *131*(2), 202-223. https://doi.org/10.1037/0033-2909.131.2.202

Mersky, H., & Nikolai, B. (1994). International Association for the Study of Pain Task Force on Taxonomy (2nd ed.). Seattle Washington: IASP pres.

Moles, A., Kieffer, B. L., & D'Amato, F. R. (2004). Deficit in Attachment Behavior in Mice Lacking the μ-Opioid Receptor Gene. *Science*, *304*(5679), 819–823. https://doi.org/10.1126/science.1095943

Olatunji, B. O., Williams, N. L., Tolin, D. F., Abramowitz, J. S., Sawchuk, C. N., Lohr, J. M., & Elwood, L. S. (2007). The Disgust Scale : item analysis, factor structure, and suggestions for refinement. *Psychological assessment*, *19*(3), 281.

Panksepp, J., Vilberg, T., Bean, N. J., Coy, D. H., & Kastin, A. J. (1978). Reduction of distress vocalization in chicks by opiate-like peptides. *Brain Research Bulletin*, *3*(6), 663–667. https://doi.org/10.1016/0004-6981(79)90244-0

Price, D. D., Harkins, S. W., & Baker, C. (1987). Sensory-affective relationships among different types of clinical and experimental pain. *Pain*, *28*(3), 297–307. https://doi.org/10.1016/0304-3959(87)90065-0

Rainville, P., Duncan, G. H., Price, D. D., Carrier, B., & Bushnell, M. C. (1997). Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science*, *277*(5328), 968–971. https://doi.org/10.1126/science.277.5328.968

Rhudy, J. L., & Meagher, M. W. (2000). Fear and anxiety: divergent effects on human pain thresholds. *Pain*, *84*(1), 65–75. https://doi.org/10.1016/S0304-3959(99)00183-9

Shaver, P., Hazan, C., & Bradshaw, D. (1988). The integration of three behavioral systems. In R. J. Sternberg & M. L. Barnes (Eds), *The psychology of love* (pp. 68–99). New Haven and London: Yale University Press.

Sharvit, G., Vuilleumier, P., Delplanque, S., & Corradi-Dell'Acqua, C. (2015). Cross-modal and modality-specific expectancy effects between pain and disgust. *Scientific Reports*, *5*, 17487. https://doi.org/10.1038/srep17487

Starr, C. J., Houle, T. T., & Coghill, R. C. (2010). Psychological and sensory predictors of experimental thermal pain: A multifactorial model. *Journal of Pain*, *11*(12), 1394–1402. https://doi.org/10.1016/j.jpain.2010.03.014

Sullivan, M., Bishop, S. R., & Pivik, J. (1995). The Pain Catastrophizing Scale. *Psychological*

Assessment, *7*, 524. https://doi.org/10.1037/t01304-000

Treede, R. D., Kenshalo, D. R., Gracely, R. H., & Jones, A. K. (1999). The cortical representation of pain [see comments]. *Pain*, *79*(2), 105–111.

Turpin, G., Schaefer, F., & Boucsein, W. (1999). Effects of stimulus intensity, risetime, and duration on autonomic and behavioral responding: implications for the differentiation of orienting, startle, and defense responses. *Psychophysiology*, *36*(4), 453–463. https://doi.org/10.1111/1469-8986.3640453

Vila, J., Guerra, P., Muñoz, M. Á., Vico, C., Viedma-del Jesús, M. I., Delgado, L. C., … Rodríguez, S. (2007). Cardiac defense: From attention to action. *International Journal of Psychophysiology*, *66*(3), 169–182. https://doi.org/10.1016/j.ijpsycho.2007.07.004

Way, B. M., Taylor, S. E., & Eisenberger, N. I. (2009). Variation in the μ-opioid receptor gene (OPRM1) is associated with dispositional and neural sensitivity to social rejection. *Proceedings of the National Academy of Sciences*, *106*(35), 15079–15084. https://doi.org/10.1073/pnas.0812612106

Williams, K. D., Cheung, C. K. T., & Choi, W. (2000). Cyberostracism: effects of being ignored over the internet. *Journal of Personality and Social Psychology*, *79*(5), 748–762. https://doi.org/10.1037/0022-3514.79.5.748

Woo, C.-W., Koban, L., Kross, E., Lindquist, M. A., Banich, M. T., Ruzic, L., … Wager, T. D. (2014). Separate neural representations for physical pain and social rejection. *Nature Communications*, *5*, 1–12. https://doi.org/10.1038/ncomms6380

Zadro, L., Williams, K. D., & Richardson, R. (2004). How low can you go? Ostracism by a computer is sufficient to lower self-reported levels of belonging, control, self-esteem, and meaningful existence. *Journal of Experimental Social Psychology*, *40*(4), 560–567. https://doi.org/10.1016/j.jesp.2003.11.006