UNIVERSITÀ DEGLI STUDI
DI MODENA E REGGIO EMILIA

Dottorato di ricerca in Neuroscienze

Ciclo XXXII

Heart of glass: cardiac autonomic vulnerability to social interaction and psychopathology

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“The greatest terror a child can have is that he is not loved, and rejection is the hell he fears. I think everyone in the world to a large or small extent has felt rejection. With rejection comes anger, and with anger some kind of crime in revenge for the rejection, and with the crime guilt—and there is the story of mankind. I think that if rejection could be amputated, the human would not be what he is.”

John Steinbeck

Summary

This research aims to study the neuro-autonomic correlates of the impairment in social functioning, found as a core component of at least two psychiatric disorders, namely Borderline Personality Disorder (BPD) and Schizophrenia (SCZ). Whereas in the former the impairment in social functioning reflects a disturbed psychological self-organization, in the latter it seems to be most related with deficit syndrome symptoms.

The polyvagal theory provides a theoretical framework to explore whether these compromised social functioning would be associated with autonomic regulation strategies that foster defensive and non-social behaviours.

According to the polyvagal theory, the physiological reactivity in response to environmental "challenges" depends, at the cardiac level, on three branches of the Autonomic Nervous System (ANS). These could be alternatively dominant and have consecutively developed during evolution as follow: (1) the un-myelinated vagal system, associated with cardiac slowing and "freezing" conducts, (2) the sympathetic nervous system, responsible for tachycardia and "fight or flight" responses, and (3) the myelinated vagal system, that acts in different ways according to the estimated threat in the environments and fosters adaptive social engagement.

The dynamic impact of the myelinated vagal fibers on the heart is reflected by the amplitude of the Respiratory Sinus Arrhythmia (RSA), a naturally occurring rhythm in the cardiac cycle at approximately the frequency of spontaneous breathing.

In the first study, using the Cyberball experiment, we investigated whether BPD patients display a peculiar pattern of changes in RSA after conditions of social inclusion and ostracism, compared with Healthy Controls (HC) and remitted Major Depressive Disorder patients (rMDD), as a clinical control group. We found that, before the task, BPD patients showed reduced resting RSA, indicating stable difficulties in social predisposition. During the task, BPD patients responded with greater physiological arousal to any social situation and with greater feelings of ostracism after

actually benign social scenarios, i.e., following social inclusion and when the ostracism experience is over.

In the second study, we measured the autonomic and psychological response to Cyberball in a sample of patients with SCZ, compared with HC. At baseline, we observed a reduced resting RSA, index of impaired social flexibility. During the task, the patients with SCZ showed a blunted perception of threat and did not report aggressive tendencies, compared to HC, in response to the condition of ostracism. In both samples, a parasympathetic withdrawal was not observed, showing that the experience of being excluded did not induce propensities toward fight/flight responding.

Overall, these findings confirmed low resting RSA that was observed across a variety of trans-diagnostic psychiatric conditions. Moreover, our results suggest that phasic changes in RSA in response to social interaction could be a trait marker of BPD.

Finally, in the third study, we investigated the interoception, conceptualized as the sense of the internal physiological condition of the body. The processing of afferent bodily signals has been linked to higher-order psychological functions such as the sense of self and emotions regulation. Specifically, recent evidence suggested that interoceptive processes might predict the autonomic regulation in a social setting. Interoceptive Accuracy (IA) was measured with a heartbeat detection task in the aggregated sample. Our results showed a reduced IA among patients with SCZ, confirming how interoceptive processes are altered in this clinical sample and should be considered as potential mediator in patients' psychosocial difficulties.

Riassunto

Questa ricerca si propone di studiare i correlati neuro-autonomici delle alterazioni del funzionamento sociale che caratterizzano il Disturbo Borderline di Personalità (DBP) e la Schizofrenia (SCZ). Nel DBP tali difficoltà riflettono un'organizzazione disfunzionale del sé; nella Schizofrenia, invece, sembrano dipendere dalla sintomatologia difettuale.

La teoria polivagale fornisce una cornice teorica per comprendere se tali alterazioni si associno a strategie di regolazione autonomica che favoriscono comportamenti difensivi.

Secondo la teoria polivagale, la reattività alle "sfide" ambientali dipende, a livello cardiaco, da tre branche del Sistema Nervoso Autonomo, sviluppate consecutivamente nel corso dell'evoluzione, alternativamente attivabili: (1) il sistema vagale non mielinizzato, responsabile della riduzione della frequenza cardiaca e di comportamenti di immobilizzazione, (2) il sistema nervoso simpatico, che determina tachicardia e risposte di "attacco-fuga", e (3) il sistema vagale mielinizzato, che si attiva in modo flessibile in base alla presenza di minacce nell'ambiente e favorisce un coinvolgimento sociale adattivo. L'impatto dinamico delle fibre vagali mielinizzate sul cuore può essere misurato con l'Aritmia Sinusale Respiratoria (ASR), un'oscillazione spontanea del ritmo cardiaco in base agli atti respiratori.

Nel primo studio, usando il paradigma sperimentale Cyberball, sono stati valutati i cambiamenti di ASR in condizioni di inclusione sociale ed ostracismo nei pazienti affetti da DBP, confrontandoli con un gruppo di Controlli Sani (CS) e con pazienti affetti da Disturbo Depressivo Maggiore Ricorrente (DDMr) in fase di remissione, inclusi come gruppo clinico di controllo. I pazienti affetti da DBP presentavano una ridotta RSA, indice di uno stato fisiologico che predispone a comportamenti difensivi già nell'approccio all'interazione sociale. Durante il gioco i pazienti affetti da DBP hanno presentato un'ulteriore riduzione dei livelli di RSA, che indica uno stato di allarme persistente, indipendente dal tipo di interazione, associato a maggiori sentimenti di minaccia anche in contesti sociali favorevoli.

Nel secondo studio le risposte autonomiche ed emotive al gioco Cyberball sono state valutate in un gruppo di pazienti affetti da SCZ, confrontandoli con un gruppo di CS. I pazienti, in condizioni di riposo, mostravano ridotti livelli di RSA, espressione di una ridotta flessibilità fisiologica in potenziali interazioni sociali. Nella condizione di ostracismo hanno riportato una minore percezione di minaccia rispetto ai CS e non hanno sviluppato tendenze aggressive verso i partecipanti da cui erano stati esclusi. In entrambi i gruppi non è stata rilevata alcuna modulazione RSA, ad indicare che nel corso dell'interazione sociale il "freno vagale" ha soppresso l'attivazione di potenziali risposte di attacco/fuga.

Tali risultati confermano che ridotti livelli di RSA a riposo si osservano in modo trans-diagnostico in diversi disturbi psichici. I cambiamenti in RSA in risposta all'interazione sociale sembrano essere distintivi del DBP.

Il terzo studio riguarda l'enterocezione, intesa come la percezione delle sensazioni interne al corpo. Il processamento dei segnali enterocettivi è stato correlato a funzioni psicologiche superiori quali il senso di sé e la regolazione emotiva. Un recente studio ha mostrato come tali processi siano associati alla capacità di regolazione autonomica nei contesti sociali. L'Accuratezza Enterocettiva (IA) è stata misurata con il task di detenzione dei battiti cardiaci, sul campione aggregato. I risultati hanno mostrato una ridotta IA nei pazienti affetti da SCZ, suggerendo un possibile effetto di mediazione dei processi enterocettivi nelle alterazioni del funzionamento sociale.

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I. General introduction

Ostracism

Belonging to a social group, in an evolutionarily perspective, has basic physical survival and reproductive benefits, moreover it seems essential for human mental health (Bernstein and Claypool, 2011). Therefore the experience of social exclusion represents a pervasive, physically and emotionally, harmful phenomenon: being rejected - defined as being explicitly told one is not wanted - or ostracized - primarily characterized by being ignored - signals a threat to social belonging for which reflexive detection is adaptive for survival (Wesselmann et al., 2012; Riva and Eck, 2016). Scientific evidences showed that the recognition of ostracism cues is so critical that even playing a game with a ball that did not actually exist and with fictitious others, in an experimental paradigm used to manipulate ostracism, raised concerns about the extent to which participants were included (Williams and Jarvis, 2006).

According to Williams' temporal model (2009) the impact of ostracism should be examined over time, because it induces consecutive responses.

He described a *reflexive stage*, with an automatic and immediate painful response, unmitigated by situational or individual differences, followed by perceived threats to the human fundamental needs (need for belonging, self-esteem, control, and meaningful existence), increases in negative emotions (sadness and anger) and aggressively responses (temptations for physical and social aggression).

Subsequently, a *reflective stage* was observed, characterized by more deliberative reactions,

that is responsive to cognitive appraisals of the situation and reflects individual differences and coping strategies. At this stage ostracized individuals should feel, think, and act in ways that will fortify the most saliently threatened need(s) and behave in ways to reestablish their inclusionary status: they do things to either remind themselves of their social connections, or that will improve their chances of belonging.

The third stage of the temporal model, called *resignation stage*, suggests that, when individuals are ostracized for long periods of time, the resources necessary for fortifying threatened needs become

depleted. Like reactance turns to learned helplessness, belonging fortification should turn to detachment and alienation, self-esteem maintenance should turn to depression, and attempts to prove worthy of attention should turn to passivity and a sense of worthlessness.

Social rejection models recreate rejection-related environments under experimental conditions. The most popular paradigm is the Cyberball game (Williams et al., 2000), a ball-tossing game in which participants believe they are playing with fellow participants, but are in fact randomly assigned to inclusion, exclusion and sometimes over-inclusion conditions and play with computer-controlled players. Cyberball is considered to be an ecologically valid paradigm for evaluating emotional reactions following social inclusion or exclusion, and was used in numerous studies involving healthy individuals (Hartgerink et al., 2015).

Physiological responses to ostracism

A controversial topic in the literature on social exclusion is the manner in which being ostracized impacts physiological reactivity.

In 2003 Eisenberg and colleagues (Eisemberg et al. 2003) showed that, in fMRI, ostracism activates some of the brain regions involved in processing physical pain (anterior cingulated cortex and right ventral prefrontal cortex), suggesting that social distress and physical pain share a common neurobiological system. Subsequent studies replicated and extended this finding, claiming that social distress "hurts", because it activates the same brain areas activated by nociceptive somatosensory stimuli (Eisemberg, 2012) and it can be modulated by analgesic drugs (Dewall et al., 2010).

However, other authors questioned this interpretation: the fact that social distress and physical pain share neurochemistry and brain activation patterns does not necessarily mean that social distress is experienced as a physical pain. They suggested that the common responses to social and physical pain may be explained by the activation of a multimodal neuro-physiological system, responsive to salient events, linked to processes underlying action preparation (Iannetti et al., 2013).

The studies that employed peripheral Autonomic Nervous System (ANS) measures in response to social exclusion, like pupillometry, galvanic skin response, infrared thermography and cardiac measures have produced conflicting results (De Rubeis et al., 2016).

Recent reports indicated that social exclusion causes diminished pupillary reaction (Sleegers et al., 2016), drop in finger temperature (Ijzerman et al., 2012), and transient slowing of heart rate (HR) (Gunther-Moore et al., 2010). This pattern seems to reflect a parasympathetic response to stress, as seen in the freezing response. Indeed, when a situation is perceived to be threatening, the brain could activate a state of parasympathetic dominance on the motor system, characterized by behavioral inhibition, relevant to perception and action preparation (Roelofs, 2017).

In contrast, other experiments found that cues of social exclusion caused peripheral sympathetic activities, documented by increases in pupillary reactivity (Silk et al., 2012), facial cutaneous temperature (Paolini et al., 2015), skin conductance levels (Murray-Close, 2011; Shoulberg et al., 2011; Sijtsema et al., 2011; Kelly et al., 2012) and HR (Murray-Close et al., 2011; Iffland et al., 2014), suggesting that exclusion activates active fight/flight responses.

The polyvagal theory

The Polyvagal Theory (Porges, 2007) provides a theoretical framework to explore the autonomic cardiac responses to ostracism.

This physiological model suggests that the cardiac reactivity in response to "challenges" depends on three branches of the ANS, that have consecutively developed during the course of evolution, and could be alternatively dominant: (1) the un-myelinated vagal system, associated with cardiac slowing, immobilization and freezing; (2) the sympathetic nervous system, responsible for tachycardia and "fight or flight" responses and (3) the myelinated vagal system, which fosters social engagement and is adaptive, acting in different ways according to the estimated threat in the environment. When the environment is safe this latter branch determines a decrease of the intrinsic HR and facilitates pro-social behaviors and interactions, while in the context of threats it causes a vagal withdrawal that allows the sympathetic activation (Porges, 2009).

The mammalian heart is characterized by a relatively strong vagal influence, via the myelinated pathways, on the heart's pacemaker (i.e., sino-atrial node). The influence of vagal brake is maintained or increased to support social engagement behaviors and reduced or removed to support the metabolic requirements for mobilization (e.g., fight/flight behaviors) (Austin et al., 2007).

Neuro-physiological evidences indicates that the dynamic functional impact of these myelinated vagal fibers on the heart is reflected by the amplitude of the Respiratory Sinus Arrhythmia (RSA), a naturally occurring rhythm in the cardiac cycle at approximately the frequency of spontaneous breathing (Porges, 2007).

Tonic RSA, usually measured during a resting state, can be conceptualized as an individual difference factor related to self and affect regulation. Higher tonic RSA is indicative of physiological flexibility that permits social engagement and more adaptive regulatory capacity in the face of environmental challenges. Low resting RSA is observed across many forms of psychopathology and several authors have suggested that low RSA could be a transdiagnostic marker of deficiencies in top-down self- and emotion-regulatory processes (Beauchaine, 2015).

Phasic changes in RSA within an individual is less well understood, because few studies have examined the vagal reactivity in response to challenge. In normative samples, increases in RSA from rest may represent positive mood states and engagement with the social environment, while decreases in RSA from a resting state (parasympathetic withdrawal) can be evoked by laboratory stressors and are associated with the induction of negative mood states (Cribbet et al., 2011). Moreover, associations between psychopathology and RSA reactivity to eliciting events are far from consistent. However, in a recent meta-analysis, Beauchaine and collegues (2019) categorized psychiatric disorders consistently with the well replicated latent structure of psychopathology derived from bifactor models, considering samples of internalizing disorders (anxiety and unipolar depressive disorders), externalizing disorders (included ADHD, substance use disorders, antisocial personality disorder and borderline personality disorder) and thought disorders (bipolar, schizophrenia spectrum, and unspecified psychotic disorders). They found that RSA reactivity

(withdrawal) was confined to studies of externalizing behaviors, reflecting propensities toward fight/flight responding in certain environmental contexts. By contrast, no such associations were found for internalizing or thought problem dimensions.

Interoception

The human body represents the source of a combination of blurred sensations coming from different districts (e.g., muscles, joints, teeth, and skin as well as the viscera) and generating diverse and diffuse bodily feelings (e.g., pain, muscle burn, visceral sensations, hunger, thirst). "Interoception" is conceptualized as the sense of this internal physiological condition of the body (Craig, 2002), combined to the representation of the same internal states within the context of ongoing activities (Craig, 2009).

Following Garfinkel and colleagues' operational definition Interoception can be declined in three distinctive and dissociable dimensions:

1. *interoceptive accuracy* (performance on objective behavioural tests of heartbeat detection);
2. *interoceptive sensibility* (self-evaluated assessment of subjective Interoception, gauged using interviews/questionnaires)
3. *interoceptive awareness* (metacognitive awareness of interoceptive accuracy, e.g. confidence-accuracy correspondence).

This distinction between behaviour and awareness is also reflected across brain networks (Barttfeld et al., 2013): the evidences suggested that neural substrates encoding discrete bodily changes, including individual heartbeats, are located in regions such as right anterior insula (Critchley et al., 2004; Fleming et al., 2010), and those underlying the perception, interpretation, and use of such information, in anterior cingulate cortex and orbitofrontal areas (Garfinkel et al., 2015; Pollatos and Herbert, 2018).

Previous research showed that Interoceptive Accuracy (IA), the process of accurately detecting and tracking internal bodily sensations, an objective empirical measure of behavioural performance, is the central construct underpinning other interoceptive measures. In fact, relationships between

interoceptive dimensions were found only in people with high IA, for whom interoceptive sensibility and awareness were related to performance of the heartbeat tracking task.

In studies consistent with this position, the insula, which has been related to the accuracy of heartbeat perception, has been implicated in emotion experience (Damasio et al., 2001), suggesting that the anterior insula and adjacent inferior frontal operculum sub-serve both emotion and interoceptive judgments (Zaki et al., 2012). These observations lend credence to the theoretical notion that the experience of emotional feeling states is supported by neural processes that underlying detection of internal bodily sensations, suggesting that interoception is a basic building block of not only physiological experience but also psychological experience (James, 1894).

Further, current neuroscience research highlights that interoceptive dysfunction may result in psychopathology (Medford and Critchley, 2014; Duquette, 2017), suggesting interoception as a potential p-factor underlying susceptibility to psychopathology (Murphy et al., 2016). Recent evidence suggests that interoception is bi-directionally related to higher-order psychological functions such as self, emotions and social processing (Löffler et al., 2018). Dysfunctional social information processing might account in part for the altered social behavior in psychopathology.

The present dissertation aims to explore cardiac vagal regulation, measured with RSA, in different psychiatric disorders, at baseline and in response to ostracism, which is considered a major psychosocial factor contributing to the development and persistence of psychopathology.

To this aim, samples of patients with externalizing (Borderline Personality Disorder- BPD), thought (Schizophrenia - SCZ) and internalizing (Major Depressive Disorder in remission phase - rMDD) disorders were involved in a Cyberball task, during which emotional and autonomic responses were recorded.

In the first session we presented the results obtained on the BPD sample compared with rMDD as clinical control group.

In the second session we reported the finding on patients with SCZ compared with a matched sample of Healthy Control (HC).

Finally, we evaluated trans-diagnostically Interoceptive Accuracy (IA), on the aggregated sample, since it could represent a moderator of affective and physiological responses to social exclusion.

II. General method

This study involved 130 participants. 90 patients seeking treatment at the outpatient Mental Health Unit of Parma, from January 2016 to September 2019, were included. 40 Healthy Control (HC) were recruited through advertisements in meeting places in the local community and among the personal staff of the University Hospital.

The Local Ethical Authority approved the study protocol, which was conducted according to the Declaration of Helsinki (World Medical Association, 2013). They were not paid for their participation and accepted to enter the study as volunteers.

All participants completed a general demographic questionnaire on age, gender, Body Mass Index (BMI), physical activity, educational level, occupational and marital status, and habitual consumption of psychotropic substances (alcohol, caffeine, and nicotine).

For the clinical groups, participants were evaluated by the Structured Clinical Interview, Clinician Version (SCID-5-CV) and Personality Disorders (SCID-5-PD) for the DSM-5 (First et al. 2016a; First et al. 2016b), two diagnostic interviews that are considered the gold standard for clinical disorders and personality disorders, respectively. The social, occupational, and psychosocial functioning was assessed with the Global Assessment of Functioning Scale (GAF) (APA, 2013).

II.a. Inclusion and exclusion criteria

Inclusion criteria were:

1) age 18-65 years;

2) native Italian speaker or proficient in Italian;

3) only for the clinical groups, participants must met the diagnostic criteria for rMDD, BPD or SCZ, assessed by the Structured Clinical Interviews for DSM-5 Clinician Version (SCID-5-CV) and Personality Disorders (SCID-5-PD) (First *et al.*, 2016a, 2016b);

4) scoring< 7 on the 21-item Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960) and < 7 in the Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959).

Participants were excluded if any of the following were present:

1. any current Axis I or any Axis II disorder diagnosis, besides rMDD, BPD or SCZ for the patients' groups;
2. any cardio-respiratory diseases and treatment that directly affect the ANS's function (e.g., sympatho-mimetic and para-sympatho-mimetic drugs, alpha and beta receptors blockers, and anti-muscarinic drugs);
3. cognitive impairment, assessed by the Wechsler Adult Intelligence Scale (WAIS) Matrix Reasoning Subtest (Wechsler, 2014).

Patients were not excluded for regular psychotropic medication use.

Participants were told that the researchers were investigating "Mental visualization and individual differences in heart rate and psychological responses." This cover story preserved the ecological validity of the experiment (Williams *et al.* 2000), as well as the psychological and physiological consequences of unexpected ostracism. Participants gave written informed consent to participation and, after completion of the experiment, were extensively debriefed and given detailed information about the study and its purposes, with the opportunity to have their data deleted should they wish so.

II.b. Psychometric assessment

Rejection sensitivity was measured with the Adult Rejection Sensitivity Questionnaire (ARSQ). Patients with Schizophrenia were evaluated also with the Positive and Negative Syndrome Scale (PANSS).

Adult Rejection Sensitivity Questionnaire (ARSQ)

Participants are asked about their concerns and expectations of rejection in hypothetical situations in which a significant othercould meet one's need for acceptance or refuse the request for help, advice, or companionship (Downey *et al.* 2006). Using a 6-point Likert scale, for each scenario, responses vary along two dimensions: (1) degree of Anxiety/concern about the outcome and (2)

Expectations of acceptance or rejection. The total ARSQ score is obtained by multiplying the ratings of the expected likelihood of rejection by ratings of concern about rejection in each situation and averaging the resulting scores. The internal consistency of the ARSQ in this sample was α = .88.

Positive and Negative Syndrome Scale (PANSS).

PANSS is a relatively brief interview, used for measuring symptom severity of patients with SCZ. The patient is rated from 1 to 7 on 30 different symptoms by a trained psychiatrist, evaluating presence and intensity of the symptoms. PANSS includes 3 sub-scales that measure positive symptoms (7 items), negative symptoms (7 items) and general psychopathology (16 items) (Kay et al., 1987).

II.c. Experimental procedure

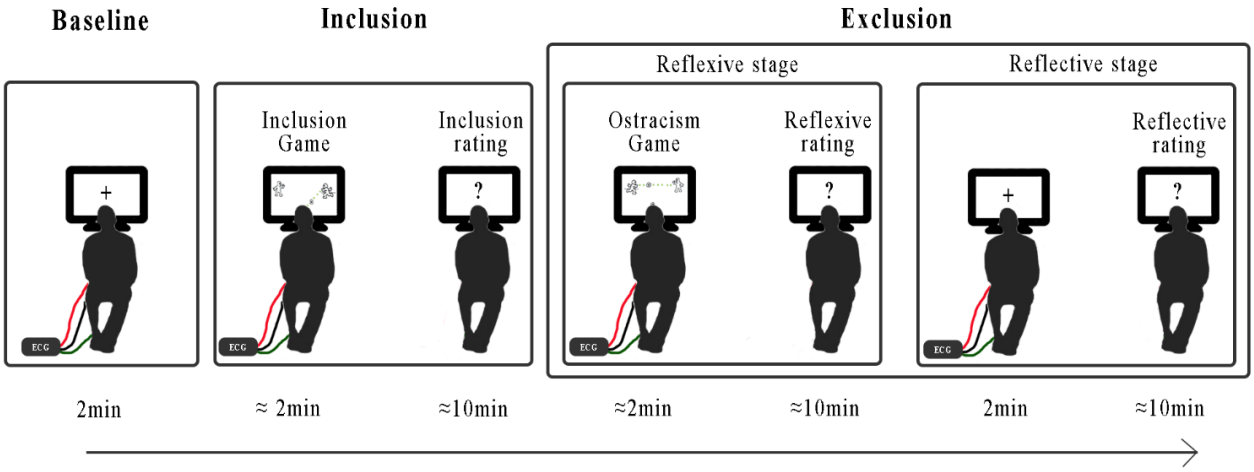
Participants were led into a quiet and soft illuminated room and were instructed to relax and to remain seated in a comfortable position. All recordings were performed in the same room with participants instructed to relax and to remain seated in a comfortable position trying to remain as still as possible during recording to minimize motion artifacts.

At the beginning of the experimental session participants completed a heart beat detection task to measure interoception.

After a short break, they were instructed to sit quietly with their eyes open and a 2-minute resting baseline ECG was recorded.

Subsequently, they participated in a *Cyberball* experiment and completed different measures of their current emotional state. ECG recordings were collected over the entire duration of the experimental session to extract phasic autonomic measures (**Figure 1**).

Figure 1. Experimental procedure.



Interoceptive accuracy (IA)

IA was measured using a heart beat detection task following the Mental Tracking Method (Schandry, 1981).

Participants were instructed to start silently counting their own heartbeat on an audiovisual start cue until they will receive an audiovisual stop cue. After one brief training session (15 s), the actual experiment started. This consisted of four different time intervals of 100s, 45s, 35s and 25s, presented in random order across participants. Participants were asked to tell to the experimenter the number of heartbeats counted at the end of each interval. Throughout, participants were not permitted to take their pulse, and no feedback on the length of the counting phases or the quality of their performance will be given.

IA score was first calculated as the mean score of four heartbeat perception intervals according to the following transformation (Schandry, 1981; Pollatos et al. 2007):

$$14 \Sigma (1- (|recordedbeats - counterbeats|)/recordedbeats)$$

According to this transformation, IA score can vary between 0 and 1, with higher scores indicating small differences between recorded and counted heartbeats (i.e., higher IA).

Tonic Respiratory Sinus Arrhythmia (RSA)

Patients were fitted with three 10 mm Ag/AgCl pre-gelled adhesive electrodes for an electrocardiogram (ECG) (AD Instruments, UK) placed in an Einthoven's triangle configuration (Ardizzi et al., 2014).

The ECG was sampled at 2 kHz and online filtered with the Mains Filter. RSA values were extracted for the entire duration of the baseline-block (120 seconds).

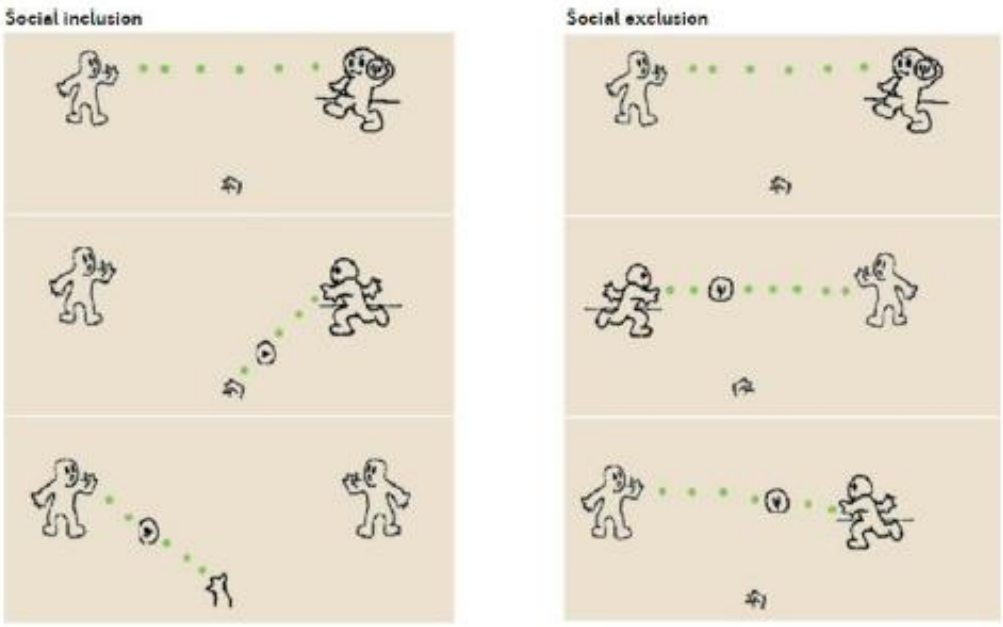
The peak of the R-wave of the ECG was detected from each sequential heartbeat. The R-R intervals were extracted and the artifacts edited by integer division or summation. Editing consisted of visual detection of outlier points, typically caused by failure to detect an R-peak (e.g., edit via division) or faulty detections of two or more peaks within a period representing the R-R interval (e.g., edit via summation). The amplitude of RSA [expressed in $\ln(\text{msec})^2$] was quantified with CMetX and calculated as the natural logarithm of the variance of heart rate activity across the frequency band associated with spontaneous respiration in adult.

Cyberball experiment

Inclusionary status was manipulated using the classic paradigm called *Cyberball* (Cyberball (version 4.0) [Software] available from https://cyberball.wikispaces.com), a virtual ball-tossing game that has been developed to induce feelings of ostracism in controlled settings (Hartgerink *et al.* 2015). Following the typical procedure (Williams *et al.* 2000), participants were told that investigators were interested in the effects of mental visualization on a subsequent task and that a good way to warm up was to engage in a mental visualization exercise with other players who were also "on-line." In reality, the other two players are not real; rather they are actually computer-controlled confederate players. All participants were enrolled in two consecutive conditions of the *Cyberball* game. Initially they were included in a belonging game (i.e., receiving the ball about a third of the time, roughly 33% of the total throws: inclusion or fair play) and then ostracized (i.e., receiving the ball once from each computer-controlled player and then never again, roughly 10% of

the total throws). The order of the inclusion-ostracism conditions was kept fixed for all participants (for a similar procedure see: Eisenberger et al. 2003) (**Figure 2**).

Figure 2. Conditions of Cyberball game.



Manipulation checks

After each *Cyberball* condition, as a manipulation check, participants rated the percentage of throws (0%–100%) they received during the game. They were then asked to report how excluded ("I felt excluded") and ignored ("I felt ignored") they felt during each *Cyberball* session. Responses were rated on 10-point scales (ranging from 1=not at all to 10=very much). The two items were combined in an overall index of feelings of being excluded and ignored. Higher scores indicate greater feelings of ostracism.

Subjective responses to the Cyberball game

Participants were asked to report their feelings three times: after *Cyberball* inclusion, immediately after *Cyberball* exclusion (i.e., reflexive stage), and 10 minutes after completing the experiment (i.e., reflective stage).

The Need-Threat Scale (NTS) measures the four fundamental needs potentially affected by ostracism in a 12-item scale: the need to have pleasant interactions with others (belonging), the need to believe others view us as worthy (self-esteem), the need to have influence over our social

environment (control), and the need to avoid our fear of death by making an impact on the world (meaningful existence) (Williams, 2009). We reversed the NTS' score, so that higher scores indicated a greater level of threat to these fundamental needs.

Rejection-related Emotions were assessed with the Rejected Emotions Scale (RES) (Buckley et al., 2004). The scale includes 22 items assessing six clusters of emotions: anger, anxiety, sadness, hurt, rejection, and happiness. Items are averaged to create an overall index of negative emotions (after reversing happiness scores). Higher scores indicate greater rejection-related negative emotions..

Aggressive temptation scale (ATS) is a measure evaluating aggressive behavior inclinations, indicating how tempted the participants would be to do aggressive behaviors towards a person they might interact with after completing the task. Responses to this measure were recorded on a 1 (Not at all tempted) to 7 (Very tempted) scale and averaged to create overall index (Buckley et al, 2004).

Autonomic responses to the Cyberball game: changes in phasic RSA

During the experiment, RSA values were extracted for the last 120 seconds of the condition-blocks (Inclusion and Ostracism) and at reflective stage (120 seconds). Phasic RSA value for each condition was measured as a change of scores between the RSA of the Condition-block (Inclusion, Ostracism reflexive stage, and reflective stage) and baseline-block RSA value.

III. Cardiac vagal vulnerability to biased social participation in Borderline Personality Disorder

III.a. Introduction

Borderline Personality Disorder (BPD) is a severe mental illness, affecting approximately 2-6% of the general population (APA, 2013). Social dysfunction represents one of the most enduring and challenging to treat feature of the disorder, which is not substantially affected by a symptomatic decrease or even remission over time (Gunderson et al. 2011). In BPD, social impairment is fostered by a unique pattern of interpersonal hypersensitivity, encompassing extensive preoccupation with real or imagined abandonment and rejection and related distrustful perceptions of others as bad, malevolent, and excluding (Gunderson, 2010; Clarkin et al. 2006). Therefore, clarifying the potential mechanisms fostering this peculiar way of processing interpersonal cues is a primary clinical and research goal in the study of BPD.

Rejection sensitivity in BPD

Rejection Sensitivity (RS) is a cognitive-affective process fostering the "disposition to anxiously or angrily expect, readily perceive, and intensely react to rejection" (Downey et al. 2004, p.668). High RS induces individuals to anticipate rejection from others and to perceive ambiguous or even innocuous cues as evidence of rejection. This increased distress in any interpersonal situation can cause negative emotional reactions and maladaptive behaviours that—ironically—may, in turn, undermine relationships by eliciting actual rejection from others (Downey & Feldman, 1996). Accumulating evidence indicates that BPD features in clinical and non clinical samples are associated with high RS (Ayduk et al. 2008; Berenson et al. 2011; Miano et al. 2013; Chesin et al. 2014; Peters et al. 2014; De Panfilis et al. 2016; Richetin et al. 2018; for a review see Poggi et al. 2019). Thus, RS could explain BPD individuals' tendency to overreact to social situations perceived as rejecting or excluding with increased interpersonal distress, negative affect, and mistrust toward others.

Along this line of research, recent studies empirically evaluated BPD patients' responses to rejection using Cyberball, a virtual ball-tossing game where participants can be socially excluded, included, or even over-included by others (Williams et al. 2006; Hartgerink et al. 2015). Interestingly, results indicate that BPD patients do not merely "over-react" to actual social exclusion; rather, they feel rejected and experience greater rejection-related negative emotions than controls following objective interpersonal inclusion (Staebler et al. 2011; Renneberg et al. 2012; Domsalla et al. 2013¸ De Panfilis et al. 2015). Moreover, BPD patients feel disconnected from others even when they face a condition of extreme interpersonal inclusion (De Panfilis et al. 2015; Weinbrecht et al. 2018). Overall, these findings suggest a "misperception of social participation": BPD patients show biased processing of social inclusion, which makes them perceive rejection even in interpersonal situations that are objectively including (e.g., the Inclusion condition in the Cyberball game).

Pathophysiological mechanisms of rejection bias in BDP

To date, most studies focused on BPD patients' subjective (i.e., explicit, self-reported) emotional reactions to the *Cyberball* experiment, while the underlying implicit pathophysiological mechanisms of this rejection bias are yet to be fully elucidated. BPD patients might have an increased sensitivity toward threatening information in the social environment, which could prevent them from efficiently and appropriately engage or disengage defense systems during social interactions.

According to the polyvagal theory (Porges, 2007), at the cardiac level, the physiological reactivity in response to environmental "challenges" depends on three branches of the Autonomic Nervous System (ANS), which have consecutively developed during evolution, and could be alternatively dominant. These are: (1) the un-myelinated vagal system, associated with cardiac slowing, immobilization, and freezing, (2) the sympathetic nervous system, responsible for tachycardia and "fight or flight" responses, and (3) the myelinated vagal system, which fosters social engagement and is adaptive, acting in different ways according to the estimated threat in the environment.

Neuro-physiological evidence indicates that the dynamic functional impact of the myelinated vagal fibers (i.e., third system) on the heart is reflected by the amplitude of the Respiratory Sinus Arrhythmia (RSA), a naturally occurring rhythm in the cardiac cycle at approximately the frequency of spontaneous breathing.

Tonic RSA, measured during a resting state, is conceptualized as an index of the inter-individual variability in social predisposition and self and affect regulation skills. Indeed, higher tonic RSA is indicative of physiological flexibility that permits social engagement and more adaptive regulatory capacity in the face of environmental challenges (Beauchaine, 2001; Tayer & Lane, 2000; Beauchaine, 2015).

Consistently, nonclinical individuals high on RS show less emotional control and more hostility in conflicts only if they are also low in resting RSA (Gyurak & Ayduk, 2008). Thus, among high rejection-sensitive individuals resting RSA might serve as a protective factor against developing interpersonal difficulties. Furthermore, BPD patients exhibit low cardiac vagal control at rest, indicating that they present a constant condition of physiological preparedness to threat and danger (Kuo & Linehan, 2009; Weinberg et al. 2009; Kuo et al. 2016; Koenig et al. 2016; Bortolla et al. 2019). This could suggest that in BPD, the RS dynamics are not buffered by an efficient vagal control, thus fostering increasing interpersonal problems and conflicts.

Phasic changes in RSA within an individual are poorly understood because studies gave a mixed interpretation of the obtained results. Among normative samples, an increase in RSA from rest is generally considered an index of positive mood states and engagement with the social environment, while decreases in RSA from a resting state (i.e., parasympathetic withdrawal) evoked by laboratory stressors are associated with the induction of negative mood states (Cribbet *et al.* 2011).

Three studies examined phasic RSA in BPD patients in response to various experimental stimuli like film clips of varying emotional content (Austin *et al.* 2007), mental arithmetic task (Weinberg *et al.* 2009), and standardized films and idiographic imagery paradigm (Kuo & Linehan, 2009). Overall, they found that BPD participants exhibited no changes (Kuo & Linehan, 2009) or

decreases in RSA during the course of the experiment (Austin *et al.* 2007; Weinberg *et al.* 2009), regardless of the conditions of each task, with a coherent and concomitant increase in the sympathetic activity (Weinberg *et al.* 2009). These results suggest that engaging in an experimental task induces, among BPD patients, a physiological state that promotes defensive behaviors, with phylogenetically older 'fight-or-flight' response, rather than a visceral state that supports self-regulation and spontaneous social engagement behaviors. Methodological issues, however, limit these results considering that RSA changes values were not normalized, despite the differences in RSA at baseline (Weinberg *et al*. 2009; Kuo & Linehan, 2009).

The present study

To our knowledge, the vagal activity in BPD has yet to be assessed during *Cyberball*. Therefore, the present study investigated whether BPD patients pose an impaired vagal control, associated with concomitant biased processing of social interactions. For this aim, we assessed BPD patients' RSA at baseline, as well as their subjective responses and changes in RSA immediately after the *Cyberball* conditions of Social Inclusion and Ostracism and 10 minutes after *Cyberball* (Reflective stage).

Based on previous research, four main predictions guided our investigation.

First, we expected that BPD patients would exhibit higher RS coupled with reduced RSA at rest (i.e., before starting the game) as compared with healthy controls and clinical controls (i.e., patients with Major Depressive Disorder in full remission). This would indicate stable difficulties in social predisposition and self-regulation in BPD, which could foster their RS-related interpersonal disturbances.

Second, we expected that BPD patients would report greater levels of fundamental needs threat and rejection-related emotions than non-BPD controls throughout the game as well as the reflective stage, confirming a biased perception of social participation.

Third, we expected that BPD patients would show a greater decrease in RSA from baseline than non-BPD controls during the *Cyberball* game, irrespective of the experimental condition. This

would indicate that BPD individuals physiologically respond to any social situation (i.e., even to objectively including and accepting interactions) as if they were threatening and excluding.

Finally, we hypothesized that BPD patients would still exhibit a reduced RSA after the completion of the experiment (i.e., at the reflective stage), indicating that they react to social participation with a prolonged breakdown of self-regulation capacities, which may prevent them to "recover" from ostracism.

III.b. Methods

Participants

This study involved 30 patients with BPD, 30 patients with remitted Major Depressive Disorder (rMDD), and 30 Healthy Controls (HC). Patients were recruited at an outpatient services from January 2016 to September 2018. HC were recruited through advertisements in meeting places in the local community and among the staff of the University Hospital.

We included MDD patients as a clinical control group because BPD and MDD are both considered being associated with problems in regulating emotions. Indeed, emotion dysregulation is assumed to be a core feature of BPD, and emotion regulation difficulties have also been documented in depressed individuals (Carvalho Fernando *et al.* 2014). We selected patients with MDD in full symptomatological remission in order to investigate whether RSA could represent a trait, stable element that could distinguish the clinical groups. Therefore we did not evaluate RSA during active phases of depression, when altered RSA is likely to represent a non-specific effect of full-blown psychopathology (Bylsma *et al.* 2014), but during the inter-episodic phases, when MDD patients may still exhibit distinctive clinical features, such as sub threshold psychopathology (Judd *et al.* 1998), peculiar personality styles (Kendler *et al.* 2006), or symptomatological scars of previous episodes (Shea et al. 1996). The literature regarding RSA and MDD is controversial and it is not clear if altered combinations of resting RSA and RSA reactivity are present also in remission phase (Chang *et al.* 2012; Yaroslavsky *et al.* 2013; Bylsma *et al.* 2014; Yaroslavsky *et al.* 2014).

Inclusion criteria and exclusion criteria are detailed in the Methods (**Session IIa**).

The total sample size collected (N=90) exceeded the minimum amount required (N=80) estimated using a priori sample size calculation, obtained for repeated-measures ANCOVA considering both within and between interactions (1-ß=0.95, α=0.05, effect size $f = 0.45$, covariates=7).

III.c. Measures and procedure

Psychometric assessment and experimental procedure were detailed in the **General method (Session IIb and IIc)**.

Statistical analysis

Descriptive statistics were performed to detail the socio-demographic and clinical characteristics of the sample.

Tonic RSA

To examine between-group differences in baseline RSA, a one-way ANCOVA was performed, entering group (BPD, rMDD, and HC) as the between-subjects factor. Bonferroni t-test was planned to explore any group effect.

Cyberball experiment

Manipulation checks. Two Repeated Measure ANOVA 3 (Group: BPD vs. rMDD vs. HC) X 2 (Experimental Conditions: Inclusion vs. Ostracism) were performed, with the post-Cyberball ratings of percentages of ball tosses received and feelings of being excluded/ignored as dependent variables.

Subjective and autonomic responses. Three Repeated Measures ANCOVA were conducted, respectively with Need-Threat Scale (NTS) scores, Rejected Emotions Scale (RES) scores, and phasic RSA values as the dependent variables, to examine how perceived threats to fundamental needs, rejection-related emotions, and the vagal measure were influenced by the experimental condition (Conditions: Inclusion vs. Ostracism vs. Reflective Stage) and by the clinical status (Group: BPD vs. rMDD vs. HC).

For the analyses where RSA was the dependent variable sex, age, alcohol, tobacco and caffeine consumption, Body Mass Index, and physical activity level were considered as covariates.

For all the models examined, multivariate tests were performed when the assumption of sphericity was violated (Mauchly's test). Simple effects analyses with Bonferroni's correction for multiple comparisons were used to evaluate significant main and interaction effects. All the analyses were carried out using SPSS software (IBM SPSS 25.0).

III.d. Results

Sample

The socio-demographic and clinical characteristics of the participants are shown in **Table 1.**

Table 1. Socio-demographic and psychometric characteristics.

	BPD	**HC**	**rMMD**	**Between-groups differences**	
	n=30	**n= 30**	**n=30**	**Main effect of factor Group**	**Post-hoc comparisons**
Age	33.2±12.07	38.9±14.65	49.27±9.96	$F_{(2,87)}$=12.98, p< .01; μ^2_p=.23	rMDD> BPD, HC (p_s<.01)
Sex (F)	27 (90%)	24 (80%)	26 (86.7%)	χ^2 (2)= 1.26, p= .53	
Education (yrs)	11.53±2.89	14.76±3.54	11.23±3.35	$F_{(2,87)}$= 10.77, p< .01; μ^2_p= .20	HC>BPD, rMDD (p_s<.01)
Matrix reasoning	16.80±2.42	20.10±2.94	18.17±3.38	$F_{(2,87)}$= 9.52, p< .01; μ^2_p=.18	HC>BPD, rMDD (p_s<.04)
Sport	12 (40%)	17 (56.7%)	11 (36.7%)	χ^2 (4)= 4.57, p= .33	
BMI	21.77±3.75	22.70±3.40	26.31±6.25	$F_{(2,87)}$=7.98, p= .01; μ^2_p=.15	rMDD> BPD, HC (p_s<.001)
Psychotropic drugs consumption					
Alcohol	17 (56.7%)	21 (70%)	7 (23.3%)	χ^2 (2)= 13.87, p=.01	
Caffeine	24 (80%)	26 (86.7%)	19 (63.3%)	χ^2 (2)= 4.84, p= .09	
Tobacco	26 (86.7%)	8 (26.7%)	5 (16.7 %)	χ^2 (2)= 35.02, p< .01	
Medications					
Mood stabilizers	25 (83.3%)	-	4 (13.3%)	χ^2 (1)= 28.5, p< .01	
Antidepressants	13 (43.3%)	-	30 (100%)	χ^2 (1)= 24.7, p< .01	
Antipsychotics	22 (73.3%)	-	4 (13.3%)	χ^2 (1)= 21.08, p< .01	
Benzodiazepines	21 (70%)	-	14 (46.7%)	χ^2 (1)= 4.05, p= .04	
Family status					
Married/living together	7 (23.3%)	16 (53.3%)	20 (66.6%)	χ^2 (6)= 16.29, p= .01	
Separated/divorced	6 (20%)	1 (3.3%)	4 (13.4%)		

Widowed	0 (0%)	1 (3.3%)	1 (3.3%)		
Living alone/with parents	17 (56.7%)	12 (40%)	5 (16.7%)		
Occupation					
Employed	16 (53.3%)	17 (53.4%)	22 (73.3%)		
Housewife	0 (0%)	4 (13.3%)	6 (20%)	χ^2 (6)= 29.13, p= .01	
Students	6 (20%)	10 (33.3%)	0 (0%)		
Unemployed	8 (26.7%)	0 (0%)	2 (6.7%)		
DSM-5 Comorbidity					
Adjustment disorder	12 (40%)	-	-		
Substance Use disorders (in full remission)	10 (33.3%)	-	-		
Alcohol Use disorders (in full remission)	3 (10%)	-	-		
Obsessive Compulsive Disorder	-	-	1 (3.3%)		
Eating disorders	2 (6.7%)	-	-		
Personality disorders	11 (36.7%)	-	3 (10%)		
Passive-aggressive	2 (6.7%)	-	-		
Paranoid	1 (3.3%)	-	-		
Histrionic	2 (6.7%)	-	-		
Narcissistic	6 (20%)	-	-		
Dependent	1 (3.3%)	-	-		
Obsessive-Compulsive	-	-	3 (10%)		
GAF	72.07±7.31	96.6±4.76	86.57±6.39	$F_{(2,87)}$= 117.11, p< .01; μ^2_p=.73	HC>rMDD>BPD(p_s< .01)
ARSQ					
Anxiety/concern	4.36± .91	3.64± 1.05	3.31± .99	$F_{(4,172)}$=9.03,p<.01; Wilk'sΛ=.68,μ^2_p=.17	BPD>rMDD, HC (p_s< .02)
Expectations	3.25± 1.2	2.40± 1.13	2.97± 1.39		BPD> HC (p= .02)
Total score	6.78±2.27	4.18±1.62	4.57± 1.68	$F_{(2,87)}$= 16.67, p< .01; μ^2_p=.28	BPD>rMDD, HC (p_s< .01)

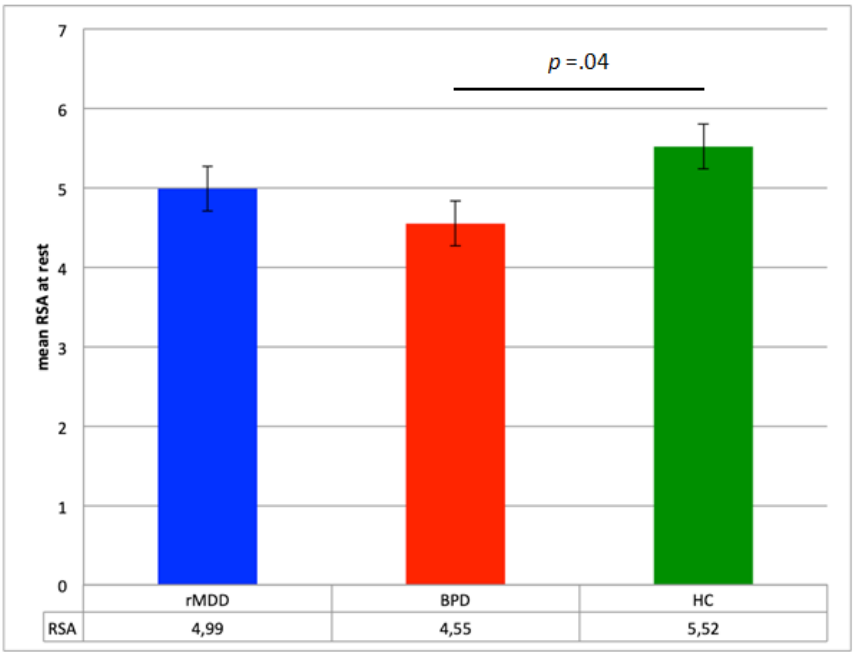
BPD: Borderline Personality Disorder, rMDD: remitted Major Depressive Disorder, HC: Healthy Control, BMI = Body Mass Index GAF = Global Assessment of Functioning, ARSQ= Adult Rejection Sensitivity Questionnaire, *χ2* = Pearson's chi-squared test

Tonic RSA

Baseline RSA differed among groups, even after controlling for age, sex, BMI, physical activity level, alcohol, tobacco, and caffeine consumption ($F_{2.80}$=3.61, p=0.03, $\eta 2_{\text{partial}}$=0.08).

Posthoc comparisons indicated that BPD patients presented lower tonic RSA compared to HC (p=0.04), while the mean RSA for rMDD patients did not differ from both BPD patients (p=0.93) and HC (p=0.40) (**Figure 2**).

Figure 2. Means for Respiratory Sinus Arrhythmia (RSA) at baseline



Cyberball experiment

Manipulation checks

There was a significant effect of the experimental *Condition* on participants' ratings of both percentages of throws received ($F_{1.85}$=40.47, p<0.01, $\eta 2_{partial}$=0.32) and feelings of being ignored and excluded ($F_{1.85}$=12.61, p<0.01, $\eta 2_{partial}$=0.13). As expected, percentage of throws received was higher in the Inclusion compared to the Ostracism condition (Inclusion 40.26±1.83>Ostracism 2.58±0.37), while combined ratings of feelings ignored and excluded were higher in the Ostracism as compared to the Inclusion condition (Inclusion 1.41±.12<Ostracism 4.28±.23). These results suggestthat the Cyberball manipulation was successful in conveying different degrees of inclusionary status, from Inclusion to Ostracism.

Importantly, there were no significant *Group by Condition* (percentage of throws received: $F_{2.85}$=1.88, p=0.16,$\eta 2_{partial}$=0.04 and feeling of being ignored/excluded: $F_{2.85}$=0.78, p=0.46, $\eta 2_{partial}$=0.02) nor *Group* effects (percentage of throws received: $F_{2.85}$=1.55, p=0.22, $\eta 2_{partial}$=0.03 and feeling of being ignored/excluded: $F_{2.85}$=1.13, p=0.33, $\eta 2_{partial}$=0.03), indicating that HC, BPD, and rMDD participants were equally cognitively aware of their inclusionary status during the game.

Subjective responses to the Cyberball game

As for NTS, there was a main within-subject effect of *Condition* (**Table 2**). As expected, overall threats to fundamental needs increased from Inclusion to Ostracism (p<0.01, CI=1.53, 2.14) and then decreased at Reflective stage when compared with the Ostracism condition (p<0.01, CI=-0.51, -0.11). However, there was also a significant main effect of *Group* (**Table 2**). Overall, BPD reported more threats to fundamental needs (although with no significant post hoc comparison). However, these main effects were better qualified by significant *Group by Condition* interaction (**Table 2**): BPDs reported higher levels of perceived threat to fundamental needs than HC and rMDD in the Inclusion condition (HC: p<0.01, CI=-1.22, -0.15; rMDD: p=0.02, CI=-1.13, -0.06), but not in the Ostracism condition (HC: p=1, CI=-0.93, 0.52; rMDD: p=0.62, CI=-1.10, 0.35) nor at Reflective stage (HC: p=0.13, CI=-1.26, 1.45; rMDD: p=1, CI=-0.81, 0.77) (effect of *Group* within the *Group by Conditi*on Interaction: F=5.75, $\eta 2_{partial}$=0.12, p<0.05). Moreover, the perception of threat to fundamental needs induced by ostracism decreases from the Ostracism to the reflective stage in HC and rMDD (HC: p<0.01, CI=0.16, 0.86; rMDD: p=0.04 CI=-0.70, -0.07), but not among BPD patients (p=1, CI=-0.40, 2.6) (Effect of *Condition* within the *Group by Condition* interaction: F=32.4, $\eta 2_{partial}$=0.43, p<0.01) (**Figure 3, Panel A)**. Similarly, regarding RES there was a main effect of *Condition*, indicating that rejection-related emotions increased from Inclusion to Ostracism (RES: p<0.01, CI=-1.40, -0.89), as well as a main effect of *Group*, reflecting greater overall rejection-related emotions in BPD than both rMDD patients (p<0.01, CI=-1.38, -0.30) and HC (p=0.01; CI=0.11, 1.19) during the game, with no difference between rMDD and HC (p=1, CI=-0.73, 0.35). However, this between-groups difference in rejection-related emotions varied depending on the experimental condition (significant *Group by Condition* interaction) (**Table 2**). BPD patients reported higher levels of negative emotions than rMDD across all the three experimental conditions (Inclusion: p=0.02, CI=0.08, 1.10; Ostracism: p<0.01, CI=0.18, 1.56; Reflective stage: p<0.01, CI=0.42, 1.69) and at Reflective stage also compared to HC (p<0.01; CI=0.27, 1.54) (**Figure 3, Panel B)**.

Autonomic responses to the Cyberball game: Changes in phasic RSA

There was a significant between-subject effect of *Group* for RSA changes (**Table 2**): BPD patients, during the experimental session, presented a greater decline in RSA from baseline as compared to HC (p=0.04; CI=-1.01,-0.14) and rMDD patients (p=0.005; CI=-1.01, -0.014) (**Figure 3, Panel C)**. We found no significant main effect of the experimental *Condition* nor *Group by Condition* interaction (**Table 2**), indicating that BPD's greater decline in RSA, as compared to baseline RSA, was independent of any specific experimental condition.

Table 2. Effect of Experimental Condition, Group Status and Their Interactions on Threat to Fundamental Needs, Emotional States and Respiratory Sinus Arrhythmia

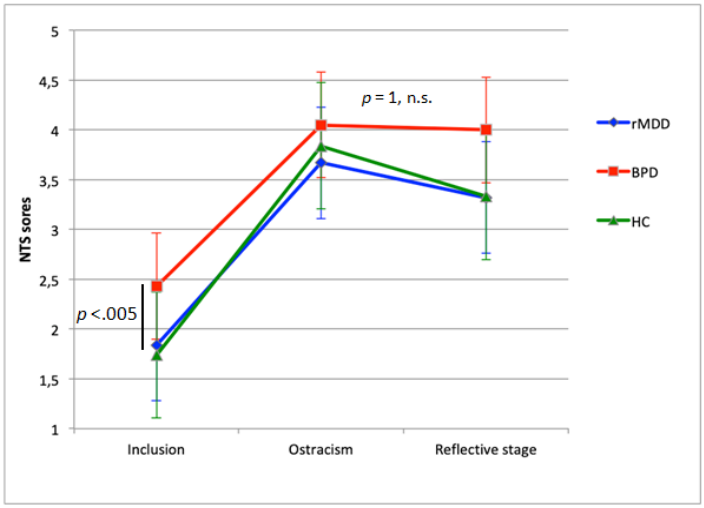
Variables	BPD	HC	rMDD	Condition	Group	Interactions Condition X Group
rNTS scores				$F_{2.86}$= 121.34$^{(a)}$ p < .01	$F_{2.87}$= 3.41 p = .04	$F_{2.87}$= 3.24 p = .04
Inclusion	2.43±.15	1.74±.15	1.84±.15			
Ostracism	4.05±.21	3.84±.21	3.67±.21			
Reflective stage	4.00±.28	3.33±.23	3.32±.23			
RES scores				$F_{2.86}$ = 64.18 p < .01	$F_{2.87}$ = 7.94 p < .01	$F_{2.87}$ = 5.28 p < .01
Inclusion	3.20±.15	2.80±.15	2.61±.15			
Ostracism	4.52±.20	3.88±.20	3.64±.20			
Reflective stage	4.61±.18	3.70±.18	3.55±.18			
RSA changes				$F_{2.79}$= .33 p = .72	$F_{2.80}$= 5.51 p < .01	$F_{2.80}$= .41 p = .67
Inclusion	-.55±.17	.04±.14	-.08±.16			
Ostracism	-.47±.15	.10±.12	.12±.14			
Reflective stage	-26±.16	.31±.13	.20±.15			

BPD: patients with Borderline Personality Disorder; HC: Healthy Controls; rMDD: patients with Major Depressive Disorder in remission; rNTS: reversed Need Threat Scale; RES: Rejection-related Emotions Scale, RSA: Respiratory Sinus Arrhythmia .

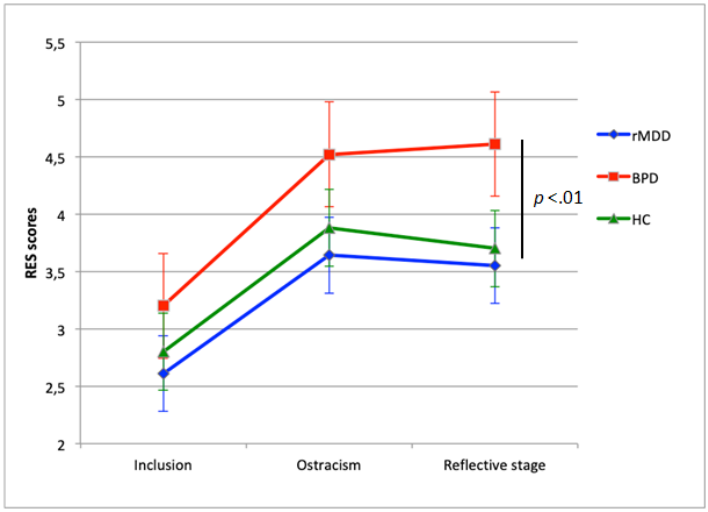
(a) Mauchly's test indicated that the assumption of sphericity had been violated for the main effect of Condition for NTS, RES and RSA changes,[NTS:$\chi^2(2)$= 19.32, p < .01; RES: $\chi^2(2)$= 60.53, p < .01; RSA:$\chi^2(2)$= 6.66, p = .04]; therefore, multivariate tests are reported

Figure 3. Means for reversed Need Threat Scale (NTS) scores (**Panel A**), Rejection-related Emotions Scale (RES) scores (**Panel B**) and Respiratory Sinus Arrhythmia (RSA) changes (**Panel C**) across test conditions.

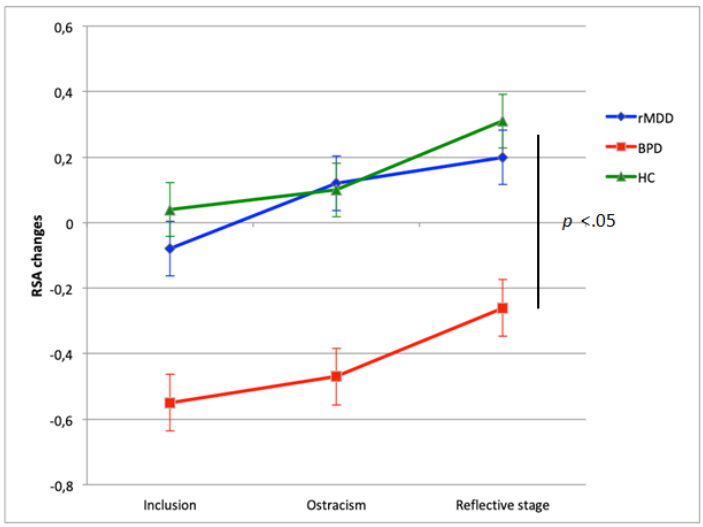
A.



B.



C.



III.e. Discussion

The present study investigated whether BPD patients' biased processing of social interactions is associated with reduced social and affective regulation and flexibility, as indexed by impaired vagal control.

Three main findings emerged. First, BPD patients presented lower tonic RSA than HC, indicating stable difficulties in social predisposition. Second, during the Cyberball task, BPD subjectively reacted to the fair condition of Inclusion with greater perception of threat to fundamental needs than non-BPD controls; furthermore, while in non-BPD controls perceived threats to fundamental needs decreased at the reflective stage, as compared to the ostracism condition, BPD did not show such "recovery" from ostracism. Finally, only among BPD patients, phasic RSA decreased compared to the baseline during the game, regardless of the experimental condition, and even after the completion of the experiment.

Regarding RSA at baseline, our results are consistent with studies showing lower tonic vagal control among BPD patients (Weinberg *et al.*, 2009; Kuo & Linehan, 2009; Kuo *et al.*, 2016; Koenig *et al*., 2016; Bortolla *et al.*, 2019). Therefore, the BPD group approached the experiment in a physiological state of preparedness for defensive behaviors, while the control groups began the game in a state that would better support social engagement behaviors. This finding is particularly relevant considering that in vulnerable high-RS populations high tonic RSA serves as a protective factor against RS-related interpersonal difficulties by buffering the "hot", automatic and maladaptive interpersonal responses fostered by the RS dynamics (Gyurak & Ayduk, 2008). Conversely, the presence of this physiological risk factor would facilitate the development of RS-related full-blown psychopathology. Consistently, in this sample, BPD patients presented not only high RS, but also low tonic RSA, which indicates a physiological vulnerability to emotional and behavioral dysregulation. Thus, results are consistent with previous studies showing that high RS is related to increased borderline psychopathology only among individuals with low self-regulatory abilities (Ayduk *et al.* 2000; Ayduk *et al*. 2008; De Panfilis *et al*. 2016).

After being ostracized, as expected, all participants perceived marked threats to fundamental needs (William *et al.,* 2006). However, in the Inclusion condition BPD patients reported a weaker sense of belongingness compared to both HC and rMDD. This indicates that BPD patients do not necessarily over-react to rejection, which is threatening for everybody; instead, they negatively react to fair, including interpersonal situations. Although BPD patients appeared cognitively aware of the different degrees of threat and correctly estimated the percentage of ball tosses received during Inclusion and Ostracism, they subjectively perceived a significantly higher level of danger in the objectively including and accepting interaction, compared with other participants. This is in line with previous *Cyberball* studies showing that BPD patients during the Inclusion condition experienced a greater sense of exclusion and a lesser sense of inclusion (Staebler *et al.* 2011; Renneberg *et al.* 2011; Domsalla *et al.* 2014; De Panfilis *et al.* 2015), and reported lower feelings of social connection and greater threats to their social needs than controls even when over-included by others (De Panfilis *et al.* 2015; Weinbrecht *et al.* 2018). Thus, BPD patients seem to react to including contexts as if they were excluding; when they are objectively included, they show belongingness ratings comparable to those reported by HC participants during the exclusion condition (Wrege *et al.,* 2019).

Furthermore, in line with the Temporal Need-Threat Model of ostracism (Williams, 2009), in this study, threatened needs quickly recovered after a few minutes from ostracism among both HC and rMDD. Conversely, BPD patients did not recover from ostracism; rather, they kept reporting feeling threatened in their need to belong. Consistently, after the end of the game, they also exhibited greater levels of rejection-related emotions than non-BPD controls. The ability to recover faster and in more functional ways from social exclusion has been found in individuals with higher levels of psychological flexibility, in terms of emotion regulation strategies (Waldeck *et al.,* 2017; Riva & Eck, 2016). By contrast, a delayed emotional recovery suggests difficulties in access to, and use of, a wider range of emotion regulation strategies to cope with ostracism experiences. Accordingly,

previous empirical evidence showed that high socially anxious participants recover their primary needs more slowly and negative feelings caused by ostracism persist longer (Zadro *et al.* 2006).

Overall, these behavioral results are in keeping with increasing evidence that BPD patients underestimate positive feed-back from others. For instance, they show lesser expectations of being socially accepted than controls and cannot adjust these expectations even after receiving actual positive feedback (Liebke *et al.*2018). Furthermore, in behavioural economics games BPD under-notice others' fair behaviour toward them, and react to that as if it was unfair by punishing them – but do not over-react to unfair behaviours of the others (De Panfilis *et al.* 2019). Moreover, after experiencing actual social acceptance they behave less cooperatively toward others (Liebke *et al.*, 2018). Finally, individuals with BPD respond with less positive emotions than controls to others' friendly behaviour (Sadikaj *et al.* 2011), and under-notice trust in others (Unoka *et al.* 2009; Fertuck *et al.* 2013; Richetin *et al.* 2018). The present findings add to this line of evidence that BPD patients perceive objectively fair, including social interactions as threatening for their fundamental human needs; further, a socially neutral condition, such as when ostracism conditions are no more at work, still elicits feelings of rejection and a weak sense of belongingness in BPD.

Finally, considering RSA changes, HC and rMDD did not show any significant deviations from tonic RSA level across the three experimental conditions. While the literature on the RSA responses to social tasks is mixed, some studies (Austin *et al.* 2007; Weinberg *et al.* 2009) suggest that tasks implementing relatively minimal social threats (Cyberball lasted about 60 seconds and involved two unknown avatars online) are not associated with any modulation in phasic RSA. This could also be the case for the experimental *Cyberball* conditions employed in this study, which ultimately favored, among HC and rMDD, the maintenance of an adaptive pro-social vagal regulation during and after the experiment, instead of a primitive defensive reaction. Conversely, BPD patients experienced a further reduction of RSA starting immediately after beginning the game. There was a stable vagal withdrawal in response to the social experiences conveyed by the task, which persisted over time, regardless of the experimental condition and even at the end of the game. This stable

drop of RSA from baseline further demonstrates that BPD patients even at the implicit, physiological level do not just over-react to ostracism as compared to non-BPD controls- they regulate the autonomic nervous system to a state that would support fight and flight responses also in the Inclusion condition and when the game is over. Thus, BPD patients are not only biased to subjectively perceive rejection even in including contexts, or when ostracism is over; they also physiologically react to such conditions with an autonomic response that signals emotion dysregulation and impedes social flexibility and prosociality. This finding is in keeping with other studies investigating the potential neurophysiologicalbases of BPD biased perception of rejection. For instance, during the Inclusion condition BPD patients show an enhanced P3b event-related potential, which usually signals social rejection (Gutz *et al.* 2015; Weinbrecht *et al.* 2018), and hyperactivate the "social pain" neural circuitry (i.e., the dorsal anterior cingulate cortex and the dorsomedial prefrontal cortex) irrespective of the experimental condition. These data suggest that BPD patients process social interactions, including those that are objectively positive, by activating neural and autonomic responses that signal rejection and threat.

Overall, these data might have implications for understanding the RS dynamics in BPD. Classic RS model postulates that the processing disposition to readily perceive and overreact to rejection may be triggered by any situation where *rejection* is a possibility (Downey & Feldman, 1996). However, our results suggest that, for BPD, the RS dynamics may be triggered by minimal instances of social interactions, which are still perceived as malevolent and unfair, thus fostering negative emotions and subsequent aggressive behaviour. In other words, BPD patients easily perceive rejection and over-react to it in any situation where *fair inclusion* is a possibility; that is, rather than being hypersensitive to rejection, they might be unsensitive to inclusion. This is in keeping with the notion of a distorted social input in BPD, which make them rely on altered social norms: BPD patients react to other's normally fair behaviour as if this was violating their social expectations (King-Casas *et al.,* 2008; King-Casas and Chiu, 2012). These findings are also consistent with clinical observations that BPD patients do not seem to benefit from generally including, "fair" and

accepting behaviour from others to regulate their emotional states, nor from a neutral condition where interpersonal rejection, although experienced in the past, is no longer occurring. According to object-relations theory (Kernberg, 1984; Yeomans *et al.,* 2015), this response pattern may reflect the patient's unconscious idealized need of finding a perfectly "accepting" relationship with others. Sadly, this intense need is unlikely to be fulfilled in reality, since human interactions may also exhibit transient difficulties or ruptures that are usually overcome by repairing trust and maintaining reciprocity. For BPD patients, though, such less-than-perfect interpersonal interactions may not be enough to fulfill their unconscious idealized need for interpersonal belonging. Thus, in the desperate attempt to protect this unconscious hope of a "perfect" relationship BPD individuals need to project one's negative affect into the others; this makes them perceive including social interactions as if they were unfair and excluding. Tragically, this threatens the possibility to feel safe and connected during "real" interpersonal exchanges.

Further research is needed in order to confirm and generalize our findings.

Our BPD and rMDD patients exhibited some socio-demographical differences, mainly related to age. This reflects the epidemiologic distribution of BPD and MDD While BPD has an onset in adolescence or early adulthood, and most patients experience symptomatic remission in a few decades (Cohen *et al.,* 2005), MDD can develop at any age, with a median age at onset at 30-40 years (Kessler et al., 2003).

Moreover, the inclusion of a clinical control group in phase remission does not clarify whether the reduced level of tonic and phasic RSA in response to *Cyberball* is specific of BPD or it represents a mere marker of the severity of actual psychopathology. An altered vagal modulation has also been reported in other clinical samples suffering from several psychiatric disorders (Beauchaine *et al.* 2015). However, our results showed that an altered cardiac vagal control seems to be a stable characteristic of BPD and not of MDD, both with comparable level of depressive symptomatology (HAMD<7). Consistently, previous studies indicated that rMDD patients, despite having prior

depression history and taking maintenance therapy, during the inter-episodic phases, seem to recover from depression also at the autonomic level (Chang et *al.* 2012; Bylsma *et al*. 2014).

Finally we could not rule out the role of pharmacotherapy. Nonetheless, independently from the diagnosis, patients with (N=43) and without (N=17) antidepressants did not differ in RSA baseline ($F_{1.51}$=.38, p=.54, $\eta 2_{partial}$=.01).

Conclusion

The results of this study indicate that BPD patients do not only feel subjectively threatened in their need to belong during accepting social encounters, as well as when the threat of ostracism is no longer present; they also show, under such circumstances, an implicit autonomic response denoting increasing emotional distress, difficulty in pro-social behaviour and breakdown of self-regulatory capacities. These findings support the view that BPD patients react, both subjectively and physiologically, to positive social contexts as if they were threatening and rejecting. Tragically, this prevents them from appreciating and reciprocating objectively inclusive, "fair" social exchanges. Thus, individuals with BPD may benefit from interventions that help them to notice and accurately recognize positive cues in social and interpersonal interactions.

IV. Social exclusion in Schizophrenia: emotional and autonomic responses

IV.a. Introduction

Interpersonal experience in Schizophrenia

Social dysfunction represents one of the basic features, a specific and autonomous psychopathological dimension of Schizophrenia (SCZ). A large number of theoretical and empirical studies have contributed on the features and causes of social dysfunction.

A phenomenological view

In classical psychopathology, "autism" is the best known construct depicting a disturbance of the self-world relation that includes detachment from outer reality associated with a predominance of an "inner life" (Stanghellini, 2017).

According to Bleuler, autism is one of the fundamental symptoms of SCZ, but it is a consequence (secondary symptom) of the splitting of psychic functions (spaltung): a defense mechanism serving to avoid conflicts between desires and reality testing, promoting the shift to inner fantasy life and entailing social withdrawal, emotional indifference, inappropriate behaviors, and idiosyncratic values and beliefs (Bleuler, 1911).

Later on Minkowski departed from Bleuler's conceptualisation and defined autism not a symptom, but a global phenomenon investing the whole person, derived from the "trouble générateur" of "loss of vital contact with reality" (Minkowski 1926, 1927). For Minkowski, autism is a way of being whose essential feature is a pragmatic deficit: autistic activity consists in the reduced capacity to interact with the external world. The self engages in fantasy in the private world of 'mental' things and observes the false self, which alone is engaged in living in the 'shared world'.

Binswanger, in his existential phenomenology (Daseinsanalyse), arrived at a similar notion of the schizophrenic way of being, defining autism as an "inconsistency of natural experience, the inability to 'let things be' in the immediate encounter with them, in other words, to reside serenely among things".

The notion of natural experience and natural evidence has been further elaborated by Blankenburg (1971). He claimed that the essence of autism consists of a "global crisis of common sense": that is, lack of an implicit understanding of the axioms of everyday life (the background of tacit knowledge shared by a social group, through which its members conceptualize objects, situations, and other persons' behaviors) and of the natural attitude (being attuned to the reality of the objective world as it appears in everyday experience).

These concepts address a pragmatic impairment where what is actually impaired is not just the possession of a sufficient stock of knowledge of the rules of the game of human sociality. Rather, the fundamental disorder is understood to be in our preconceptual and precognitive grip on social situations, a kind of prereflexive 'indwelling' in the social world (Parnas, 1991).

Similarly Kimura Bin argued that only such a relational understanding of the self renders schizophrenic experiences possible. According to Kimura (Kimura 2001), subjectivity is constituted by a double "in-between" ("aïda"), that is, between one and the other self and between the self and the world. Autism implies a disturbance of the ability to perceive the existence of others and to see their mental structure as similar to one's own; make emotional contact and establish mutual relationships; intuitively understand the manifestations of mental life of other persons, and communicate with others using the shared meaning structures in a context-relevant manner.

Therefore, from the view of clinical phenomenology, this autism reveals itself in a relational process between the autistic person and the outer world: it is not an inherent characteristic of an isolated symptom carrier, but refers to a global defective cognitive/affective attunement between the patient with SCZ and his environment (Stephensen and Parnas, 2018)

A cognitive view

Cognitivism is the dominant approach to empirical research on social dysfunction in SCZ. Initially, studies in SCZ have focused on neurocognitive function. The results consistently demonstrated that neurocognitive deficits are found in almost all patients with SCZ and are a core feature of the disorder (Insel et al, 2010).

However, in the last decade, cognitive neuroscience studies in SCZ shifted attention from neurocognitive function towards social cognition, a relatively new concept, which seems to be a better predictor of social abilities and real world function (Charernboon and Patumanond, 2017). Social cognition refers to the mental operations underlying social interaction and includes various and still debated psychological constructs (Hogarty and Flesher, 1999). These social cognitive impairments interfere with social connections and are strong determinants of the degree of impaired daily functioning in such individuals.

The NIMH consensus statement on social cognition in SCZ (Green et al., 2019) showed the main impairments of social cognition in persons with SCZ fits into the following 5 areas of research.

1. Theory of mind, also called mental state attribution, typically involves the ability to infer intentions, dispositions, and beliefs of others.
2. Social perception represents one's ability to identify social roles, societal rules, and social context. In social perception tasks, participants must process nonverbal, paraverbal, and/or verbal cues to make inferences about complex or ambiguous social situations.
3. Social knowledge, also called social schema, refers to awareness of the roles, rules, and goals that characterize social situations and guide social interactions.
4. Attribution bias or style reflects how people typically infer the causes of particular positive and negative events and of emotional behaviors. Research involving persons with schizophrenia has also focused on hostile attributional biases or the tendency to attribute hostile intentions to others' actions.
5. Emotional processing refers broadly to perceiving and using emotions. One influential model of emotional processing defines emotional intelligence as a set of 4 components, including identifying emotions, facilitating emotions, understanding emotions, and managing emotions.

Different bodies of evidences have linked the deficit in social cognition in SCZ to structural and functional disturbances in the so-called "social brain". This incorporates a set of brain areas

distributed in the frontal, parietal, and temporal regions that are integrated into extensive neural networks associated with various aspects of cognition. The medial prefrontal cortex, the adjacent anterior cingulate cortex, the temporo-parietal junction, the superior posterior temporal cortex, and the temporal poles make up the core of the social brain involved in social cognition.

Recently Nelson and Sass (2017) pointed to a convergence of phenomenological and cognitive approaches, suggesting that neurocognitive disturbances may constitute the neural correlates of an abnormal sense of basic selfhood and, by implication, of experience of others and the world.

According with these authors, the fundamental impairment in the dimension of intersubjectivity (disorders of social and interpersonal functioning and inappropriate behaviour), the compromising shared engagement with the world ('common sense' or 'rules of the game'), the pre-reflective attunement with others would naturally result in the measured social cognition difficulties.

Cardiac vagal control in SCZ

Individuals with SCZ face significant challenges in daily functioning, and although social cognition predicts how well patients respond to these challenges, associated physiological mechanisms remain unspecified. The polyvagal theory (Porges, 2007) highlights regulatory mechanisms within the cardiovascular system that promote flexible engagement with situational demands and that support adaptive social and emotional behaviors.

Research has shown reduced cardiac vagal tone in SCZ patients, regardless of medication status, and in their healthy relatives (Bär et al., 2010, 2007; Mujica-Parodi et al., 2005; Clamor et al, 2016). Indeed, cardiac vagal tone has been associated with clinical ratings of global functioning in SCZ (Fujibayashi et al., 2009). As suggested by polyvagal theory, cardiac vagal tone reflects an individual's capacity to engage flexibly with the surrounding environment, then RSA should exert a significant impact on adaptive functional outcomes for SCZ patients, as they perform in the workplace, interact socially, or engage in daily activities.

A recent study (Hamilton et al., 2014) focused on the relation between social cognition and functional outcome in patients with SCZ. In line with previous evidence (Horan et al., 2012) the

authors found that social cognition is predictive of functional outcome in SCZ, but the association was significantly moderated by RSA. Specifically, among patients with poor social cognition, functional outcome was found to be largely contingent upon RSA. In contrast, in patients with strong social-cognitive skills, functional performance was independent of RSA. Thus, self-regulatory capacity and psychological flexibility, as indexed by RSA, may compensate for poorer social– cognitive abilities in individuals with SZ.

However, parasympathetic dysfunction is not specific to SCZ: aberrant autonomic function has been observed consistently among individuals with various forms of internalizing and externalizing psychopathology, indicating susceptibility for cognitive and affective symptoms shared across neuropsychiatric disorders (Beauchaine, 2015).

Few studies investigated the autonomic reactivity to social and non-social tasks in patients with SCZ. Liu et al. (2016) reported a diminished cardiac autonomic reactivity to deep breathing in patients with SCZ and their unaffected relatives. Andersen et al. (2018) found that an acute psychosocial stressor (a 5-minute mock job interview and 5 minutes of challenging serial subtraction) induce blunted parasympathetic reactivity and abnormal arousal regulation in response to stress exposure in patients with SCZ. Valkonen-Korhonen et al. (2003) showed that the patients' HRV remained unaltered during a cognitive tasks (Wisconsin Card Sorting Test), whereas in controls the HRV diminished with increasing mental load of the task. Recently, Beauchaine and colleagues (2019) evaluated associations between RSA reactivity and empirically derived structural categories of psychopathology—including internalizing, externalizing, and thought problems, suggesting that RSA withdrawal was not associated with thought problem dimensions.

Ostracism and schizophrenia

Individuals with SCZ represent a clinical population that may be especially affected by social exclusion. However, few prior studies examined the effects of ostracism, experienced in experimental settings, in individuals with SCZ.

In a behavioral Cyberball study, Perry et al. (2011) showed that, analogous to their non-clinical counterparts, being socially excluded elicits an automatic, reflexive response in patients with SCZ and schizoaffective disorder. Moreover individuals with SCZ showed less recovery than those in the control group, suggesting that the negative impact of social exclusion lasts longer. This effect has been related to the use of maladaptive coping strategies such as rumination or to the lack of acceptance of the ostracism experience, which, paradoxically resulted in maintenance of negative thoughts and feelings.

In another study, Engel et al. (2015) found that patients with SCZ and schizoaffective disorder tended to report significantly less intense positive emotions than healthy controls related to social inclusion in Cyberball, suggesting that in real-life social situations patients would decide to refrain from social interactions because they anticipate that these will not make them happy.

More recently, Reddy et al. (2019) showed that, following social exclusion, both individuals with SCZ and HC decreased psychological need security, but controls experienced more threat to their sense of security than did patients, suggesting that individuals with schizophrenia, as a group, may self-report less psychological pain than controls owing to exclusion. According with the authors, this pattern may indicate that social exclusion is less familiar, and therefore more salient and painful, for controls, while chronic experiences of social exclusion, which are characteristic of many people with SCZ, may have persistently threaten fundamental psychological needs, altering psychological and cognitive responses.

Other studies evaluated the effect of social exclusion on positive symptoms of SCZ, specifically on paranoid ideation. Overall they found that, after social exclusion, non clinical samples and neurosis patients reported a higher increase in subclinical paranoid beliefs compared to the control groups (Westermann et al., 2012, Kesting et al, 2013; Kim et al., 2014). Sundag et al (2015), evaluating the formation of delusions, found that patients with persecutory delusions presented higher increases in paranoia following the social exclusion condition compared with HC, consistently with the postulated sensitivity to stress that has long been implicated in the pathogenesis of psychosis.

According with Wesselmann (2012) delusion-prone individual who experiences him- or herself as being excluded in a game, will attempt to down-regulate his or her negative emotions via reappraisal, and in doing so is likely to jump to conclusions that are congruent with his or her interpersonal schema (e.g., "Others are bad") resulting in a failed reappraisal (e.g., "They are excluding me on purpose").

Also fMRI study studies investigated the neural mechanism of patients' experiences of social rejection, for exploring the neural correlates of social problems in SCZ. In HC the activation of the mPFC/vACC in response to social exclusion has been repeatedly reported (Eisemberg et al., 2003) in many Cyberball studies. In contrast, patients with SCZ did not exhibit this response (Gradin et al., 2010), with the magnitude of the abnormality correlating with positive symptom severity. Lee et al. (2014) showed that another virtual interactive setting, the refusal of a handshake, successfully induced feelings of social rejection in patients with SCZ and in HC. However the refusal of a handshake activated the right superior temporal sulcus in the control group and the frontopolar cortex in the SCZ group. The authors interpreted these findings as expression of the presence of mentalizing deficits and altered modulation of social information processing in response to social feedback, highlighting the mPFC as a potential neural substrate of interpersonal difficulties in schizophrenia.

To our knowledge no previous study investigated whether patients with SCZ modulated their subjective feelings and vagal myelinated system in a Cyberball task.

The present study

The present study aims to explore the emotional and neuro-autonomic responses to ostracism in patients with SCZ, compared with a sample of healthy controls.

For this objective we measure the cardiac vagal control at baseline, hypothesizing that patients SCZ would present reduced a cardiac vagal tone (RSA baseline), indices of difficulties in social predisposition.

Then we assessed patients' subjective responses and changes in RSA immediately after the Cyberball conditions of Social Inclusion and Ostracism and 10 minutes after Cyberball (Reflective stage).

We hypothesize that patients with SCZ would report a blunted perception of threat to fundamental needs and reduced aggressive tendencies compared with HC, without any physiological fight and flight response (RSA withdrawal), suggesting that they would not adequately perceive and deal with potential social threats.

IV.b. Method

Participants

This study involved 30 patients with SCZ and 30 Healthy Controls (HC), matched for age and gender. Patients were recruited at an outpatient services from January 2018 to September 2019. HC were recruited through advertisements in meeting places in the local community and among the staff of the University Hospital.

Inclusion criteria and exclusion criteria are detailed in the **General methods** (**Session IIa)**.

Measures and procedure

Psychometric assessment and experimental procedure were detailed in the **General methods (Session IIb and IIc)**.

Statistical analysis

Descriptive statistics were performed to detail the socio-demographic and clinical characteristics of the sample.

Tonic RSA

To examine between-group differences in baseline RSA, a one-way ANCOVA was performed, entering group (SCZ and HC) as the between-subjects factor. Bonferroni t-test was planned to explore any group effect.

Cyberball experiment

Manipulation checks. Two Repeated Measure ANOVA 2 (Group: SCZ vs. HC) X 2 (Experimental Conditions: Inclusion vs. Ostracism) were performed, with the post-Cyberball ratings of percentages of ball tosses received and feelings of being excluded/ignored as dependent variables.

Subjective and autonomic responses. Three Repeated Measures ANCOVA were conducted, respectively with Need-Threat Scale (NTS) scores, Aggressive Temptation Scale (ATS) scores, and phasic RSA values as the dependent variables, to examine how perceived threats to fundamental needs, aggressive temptation, and the vagal reactivity were influenced by the experimental condition (Conditions: Inclusion vs. Ostracism vs. Reflective Stage) and by the diagnosis (Group: SCZ vs. HC).

For the analyses where RSA was the dependent variable sex, age, alcohol, tobacco and caffeine consumption, Body Mass Index, and physical activity level were considered as covariates.

Simple effects analyses with Bonferroni's correction for multiple comparisons were used to evaluate significant main and interaction effects.

Responses to ostracism and symptom severity

Bivariate associations between subjective (NTS) and physiological (RSA reactivity) measures during the Cyberball game and symptom severity, evaluated with PANSS, were explored using the classic Pearson's r coefficient of linear correlation.

All the analyses were carried out using SPSS software (IBM SPSS 25.0).

IV.c. Results

Sample

The socio-demographic and clinical characteristics of the participants are shown in **Table 3.**

SCZ patients on average showed lower scores in WAIS Matrix reasoning subtest which measures cognitive performance. They had a lower level of education, they were unemployed and more often

they lived alone, compared to HC. These results account for a reduction of the global functioning levels, as shown by the lower GAF scores of SCZ patients. The HC were more likely to use alcohol and caffeine compared to SCZ patients.

Table 3. Socio-demographic and psychometric characteristics of the sample

	SCZ n=30	**HC** n= 30	*t/ χ2*	*p*
Age	38.17±10.5	37.53±12.41	*t*=0.21	*p*=.832
Sex (F)	8 (26.7%)	14 (73.3%)	*χ2*=2.58	*p*=.108
Education (yrs)	10.43±3.38	15.66±2.66	*t*=6.67	*p*<.001
BMI	27.08±5.59	23.79±3.24	*t*=2.78	*p*=.007
Matrix reasoning	17.23±3.72	21.13±2.87	*t*=4.54	*p*<.001
Sport	7 (23.3%)	19 (63.3%)	*χ2*=9.77	*p*=.002
Family status			*χ2*=20.22	*p*<.001
- married	1 (3.3%)	14 (46.7%)		
- living together	1 (3.3%)	4 (13.3%)		
- separated/divorced	2 (6.7%)	0 (0%)		
- single/living alone	26 (86.7%)	12 (40%)		
Occupation			*χ2*=24.37	*p*<.001
- employed	7 (23.3%)	16 (53.3%)		
- part-time	6 (20%)	2 (6.7%)		
- students	2 (6.7%)	8 (26.7%)		
- housewife	0 (0%)	3 (10%)		
- unemployed	15 (50%)	1 (3.3%)		
Psychotropic drugs				
- Alcohol consumption	13 (43.3%)	21 (70%)	*χ2*=4.34	*p*<.037
- Caffeine consumption	16 (53.3%)	26 (86.7%)	*χ2*=7.94	*p*=.005
- Tobacco consumption	10 (33.3%)	8 (26.7%)	*χ2*=.32	*p*=.573
Duration of Illness (yrs)	12.97±10.2	-		
Age Onset	25.4±6.39	-		
GAF	61.17±13.06	98.1±4.03	*t*=14.79	*p*=.008
Treatment				
- AP	12 (40%)	-		
- AP+AD	7 (23.3%)	-		
- AP+BZD	4 (13.3%)	-		
- AP+AD+BZD	6 (20%)	-		
- AP+mood stabilizers	1 (3.3%)	-		
PANSS				
Total	77.15±13.76			
Positive scale	15.23± 4.77			
Negative scale	21.04±5.04			

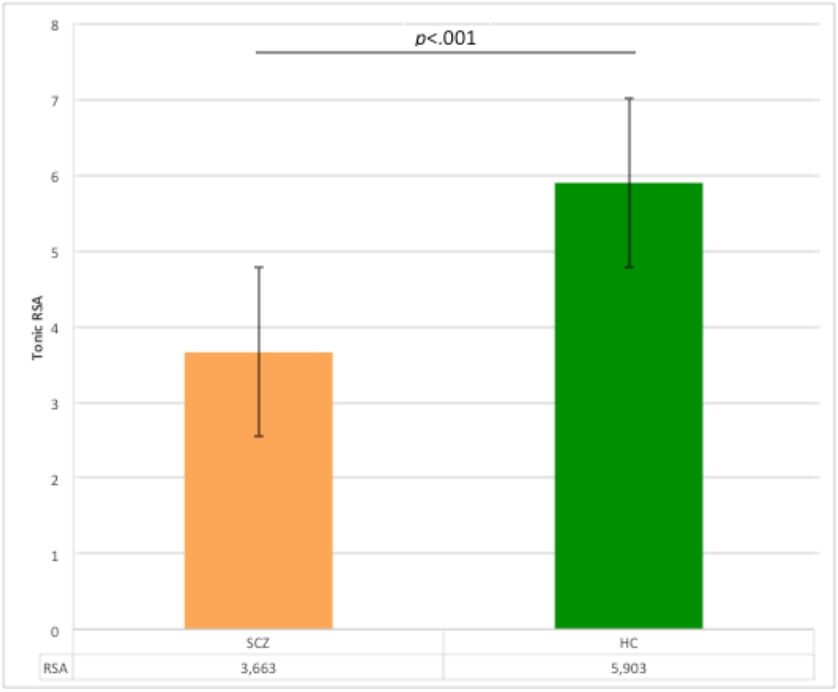
General Psychopatology scale	40.11±8.32

SCZ: Schizophrenia, HC: Healthy Control, BMI = Body Mass Index GAF = Global Assessment of Functioning, PANSS: Positive and Negative Syndrome Scale $\chi 2$ = Pearson's chi-squared test; *t* = T-test

Tonic RSA

Baseline RSA differed amongst the two groups, (respectively, t=-4.576, CI95%=-3.219, -1.260, p<0.01). SCZ patients presented lower tonic RSA (3.663±2.286) compared to HC (5.903±1.401). These differences persisted even after controlling for age, sex, BMI, physical activity level, alcohol, tobacco, and caffeine consumption (F1.59=11.054, p<0.01) (**Figure 4**).

Figure 4: Means for Respiratory Sinus Arrhythmia (RSA) at Baseline



Cyberball experiment

IV.d. Manipulation check

Data highlighted a significant effect of the experimental Condition (Inclusion, Ostracism and Reflective stage) on participants' ratings of percentage of throws received (F1.58=275.027, p<0.001) and on the feeling of being ignored and excluded (F1.58=139.109, p<0.001).

This shows that the Cyberball manipulation was successful in modulating different degrees of social perception, from inclusion to ostracism, nonetheless with a different degree of involvement in the two groups.

The effect of the Condition is associated with a significant *Group by Condition* interaction both in the appraisal of throws received, and in the perception of being excluded/ignored (respectively, $F1.58=11.738$, $p<0.001$ e $F1.58=8.681$, $p<0.005$). Compared to the percentage of throws received, SCZ patients perceived to have received the ball more often in the Inclusion condition than HC (SCZ=51.5% vs HC=32.7%, $p<0.001$, CI95%=-27.984, -9.616), reporting a comparable number throws in the Ostracism condition (SCZ=6.33% vs HC=3.33%, $p=0.095$, CI95%=-0.166, -6.833). In regards to the perception of being excluded and ignored, SCZ group reported similar scores to HC in Inclusion condition (SCZ=1.517 vs CS=1.517, $p=1$), however, feeling less excluded than HC during Ostracism (SCZ=3.650 vs CS=5.067, $p=0.007$).

IV.e. Subjective responses to the Cyberball Game

Mauchly's test conducted on NTS and ATS scores showed a violation of sphericity assumption (NTS: $\chi2=9.495$, p=0.009; ATS: $\chi2=44.605$, $p<0.001$), Hence, the degrees of freedom were adjusted using Greenhouse-Geisser correction.

Both for NTS and ATS scores, we found a significant main effect of the experimental *Condition* on the self-perception of the exclusion, a significant *Group by Condition* interaction, without a significant main effect of *Group* (**Table 4**).

Post-hoc analysis showed that SCH patients presented a lower perception of threats to fundamental needs in the Ostracism condition ($p=0.03$) and at the Reflective stage ($p=0.05$), compared to HC. However, NTS scores in the Ostracism condition, in both Reflective and Impulsive stage, were significantly higher than NTS scores of the Inclusion condition (respectively, $p<0.01$ e $p=0.024$) **(Figure 5, Panel A).**

As for ATS scores, instead, SCZ patients presented lower levels of aggression in the Ostracism condition (p=0.004) and at the Reflective stage (p=0.033), however they did not report a significant increase in aggressive behaviour from Inclusion to Ostracism (p=1) (**Figure 5, Panel B**).

These differences did not seem depending only on an effect of an experimental group, but also on a specific response to social interaction conditions.

Autonomic responses to the Cyberball game: Changes in phasic RSA

Our results did not showed significant variation on the Parasympathetic Nervous System response, measured with RSA changes in the different experimental conditions, compared to baseline RSA, without a significant main effect of *Group by Condition* interaction, nor significant between-subject effect of *Group* (**Table 4**), indicating that the participation in a Cyberball Game did not significantly modified cardiac vagal activity among both SCZ patients and HC (**Figure 5, Panel C**).

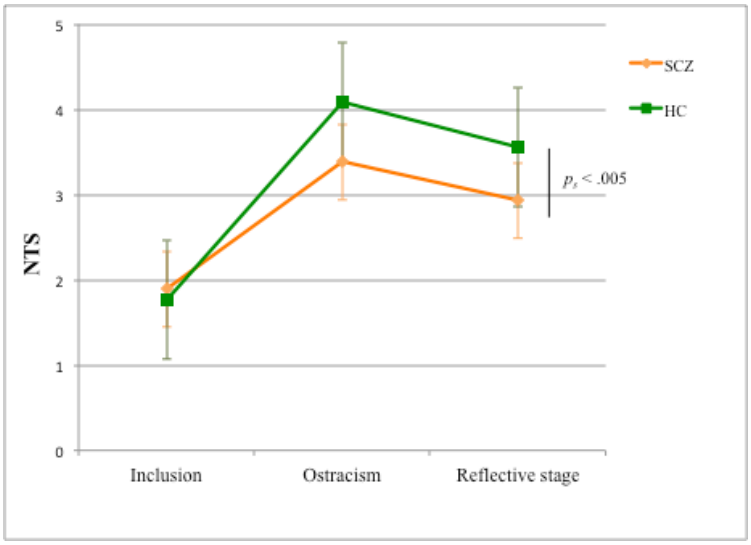
Table 4. Effect of experimental condition, group status and their interactions on perceived Threat to Fundamental Needs, Aggressive Temptation and Respiratory Sinus Arrhythmia

Variables	SCZ	HC	Condition	Group	Interactions Condition X Group
rNTS scores			F2.58=87.058, p<0.01	F1.58=3.077, p=0.085	F2.58=4.635, p=0.016
Inclusion	1.89±.15	1.77±.15			
Ostracism	3.38±.22	4.08±.21			
Reflective stage	2.93±.23	3.55±.23			
ATS scores			F2.58=20.203, p<0.01	F1.58=3.618, p=0.062	F1.58=11.630, p<0.01
Inclusion	2.15±.13	2.02±.13			
Ostracism	2.30±.17	3.05±.17			
Reflective stage	2,26±.19	2.85±.19			
RSA changes			F2.51=0.623, p=0.538	F1.51=0.720, p=0.400	F2.51=0.18, p=0.835
Inclusion	-.14±.14	-.02±.14			
Ostracism	-.05±.13	.05±.13			
Reflective stage	-.04±.13	.18±.13			

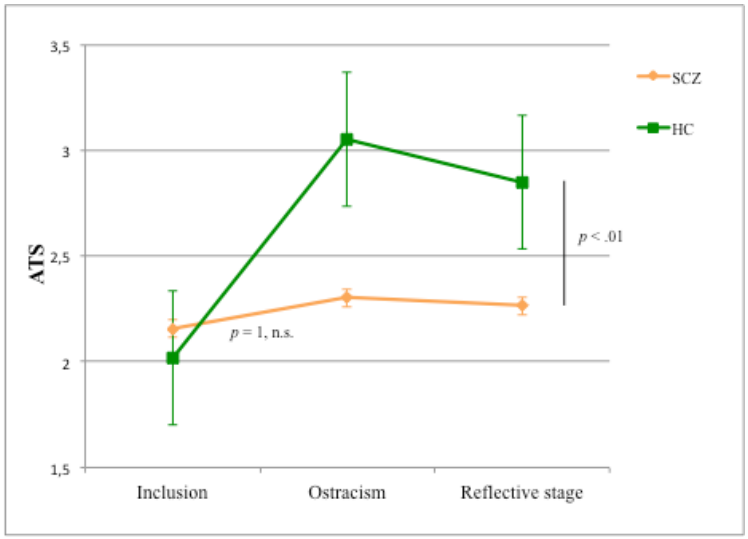
SCZ: Schizophrenia, HC: Healthy Control, rNTS: reversed Need Threat Scale, ATS: Aggressive Temptation Scale, RSA: Respiratory Sinus Arrhythmia

Figure 5. Means for reversed Need Threat Scale (NTS) scores (**Panel A**), Aggressive Temptation Scale (ATS) scores (**Panel B**) and Respiratory Sinus Arrhythmia (RSA) changes (**Panel C**) across test conditions.

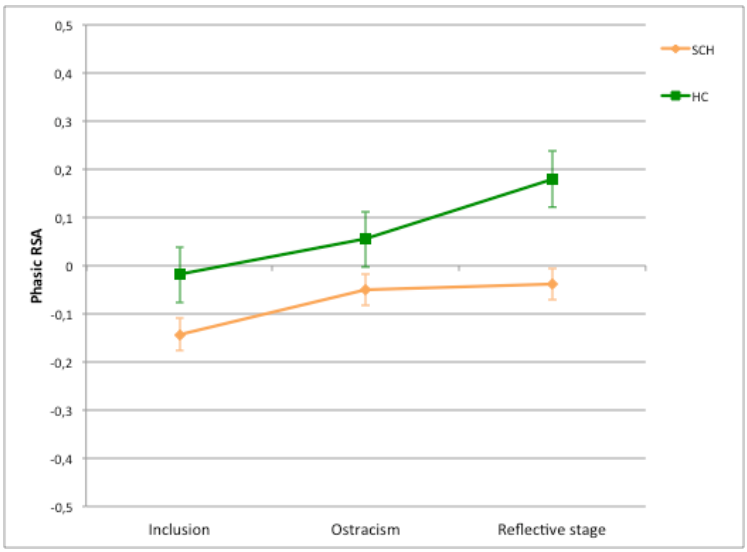
A.



B.



C.



Responses to ostracism and symptom severity

No significant correlation was found between emotional or physiological responses reported after Cyberball game and any scores in PANSS sub-scales.

IV.f. Discussion

The results of the study showed that patients with SCZ present a low cardiac vagal control at rest (low tonic RSA), compared with HC. By challenging the participants with two consecutive conditions of a Cyberball task (social inclusion and ostracism), patients with SCZ subjectively perceived fewer threats to the human fundamental needs and did not develop aggressive tendencies, in response to ostracism, compared with the non-clinical participants. In both groups we did not found any modulation in RSA reactivity during the experimental task.

This finding confirmed that low RSA in condition of rest characterizes trans-diagnostically most forms of psychopathology (Beauchaine et al., 2019). In line with previous studies on patients with Schizophrenia (Hamilton et al., 2014; Bär et al., 2010; Mujica-Parodi et al., 2005; Demaree et al., 2004; Beauchaine, 2001; Ingjaldsson et al., 2003; Rechlin et al., 1994) the reduced cardiac vagal tone could be interpreted as an unspecific index of difficulties in social predisposition. The reduced parasympathetic vagal activity at baseline is consistent with an autonomic profile indicative of deficit in physiological flexibility (Cribbet et al., 2011), supporting defensive rather than engagement behaviors in calm, neutral situations (Andersen et al., 2019), and expression of emotion dysregulation (Beauchaine et al., 2015; Caspi, 2014).

Considering the subjective emotional responses, the blunted perception of threat to human fundamental needs in patients with SCZ has been found in a previous published studies (Reddy et al., 2019): also these authors observed that on the measure of psychological need security, both patients with SCZ and HC showed a decreased following exclusion, controls experienced more threat to their sense of security than did patients. In line with the study of Perry et al. (2011) we observed, among patients with SCZ, the immediate, painful impact of ostracism. However, in

contrast with this study, we found that the intensity of this reaction was lower compared with HC and did not last longer. The reason for the discrepancy could be methodological: in that study participants were tested on two occasions separated by approximately six months and they were included during the first session and ostracized during the second session.

The pattern of response that we observed supports the Need Threat Model of Ostracism (1997, 2001). Williams (2007) proposes a third stage of responses to ostracism, whereby individuals who are chronically exposed to social rejection begin to accept alienation and isolation. It is suggested that those who reach this stage may give up on seeking out social contact and approval, and withdraw in order to avoid the possibility of further exclusion. Even if patients with SCZ still reported to feel threat when faced with social exclusion, this pattern may indicate that social exclusion is more familiar, and therefore fewer salient and threatening, compared with HC.

Accordingly, the sociometer theory (Leary et al., 1995) proposes the existence of a psychological mechanism (a "sociometer") that enables individuals to detect potential rejection via others' reactions; a properly working sociometer affords a person predictive control over an interaction. Our result suggests that patients with SCZ can rely on a hypoactive sociometer, relatively insensitive to changes in relational values. Although instances arise in which a person ought to disregard other people's reaction, chronically doing so leads the person to be ostracized by everyone because he or she fails to react intelligently to situations that ought to convey low or declining relational value (Leary and Guadagno, 2011).

Moreover we observed that patients with SCZ did not report to develop any aggressive tendencies towards the excluding participants, while HC showed a proper increase of their aggressive tendencies during ostracism, that decline at reflective stage. Developing aggressive tendencies is generally considered an adaptive response. Again, according to Williams's (1997, 2001) model of ostracism, an ostracized individual that experience an immediate threat to four basic human needs will consequently be motivated to restore those needs. The needs may best be fortified by pro-social behaviors, such as conformity (Williams, Cheung, & Choi, 2000) social compensation (Williams &

Sommer, 1997); unconscious mimicry (Lakin & Chartrand, in press), and increased attention to and processing of social information. However, when control is sufficiently thwarted, desires to fortify control can outweigh desires to belong, thus allowing aggression to be a functional response (Warburton & Williams, 2005; Tedeschi, 2001; Chow et al., 2008; Wesselmann et al., 2010). Therefore this lack of response, in patients with SCZ, could be expression of the failure to recognize salient threatening stimuli and, consequently, to engage in prosocial and adaptive behaviors oriented to a social re-inclusion.

Finally, we did not observe any modulation in phasic RSA, during Cyberball, in both HC and patients with SCZ.

Interpreting our findings, we suggest that HC did not present any modulation because their baseline physiological state, characterized by high vagal influence on the heart, has retained during the task, in order to support spontaneous social engagement behaviors (Austin, 2007). Our results, in fact, suggest that HC were able to easily access to emotion regulation strategies that maintain parasympathetic tone. Davis et al. (2016) reported similar conclusions in a previous study on children. All the children watched a sad and a scary film and a group of them received instructions to deploy a target strategy to manage sadness/fear while they watched. Children assigned to use an emotion regulation strategy showed greater RSA augmentation from baseline than children in the control condition. As reported above, discussing our results on patients with BPD, we observed that a tasks implementing relatively minimal social threats (Cyberball lasted about 2 minutes and involved two unknown avatars online) ultimately favored, in HC, the maintenance of an adaptive pro-social vagal regulation during and after the experiment, instead of a primitive defensive reaction.

Also patients with SCZ did not presented modulation in RSA during the game that remained low for the entire duration of the task. This finding replicated the suggestion of the recent meta-analysis conducted by Beauchaine and colleagues (2019) that stated that “RSA withdrawal was confined to studies of externalizing behaviors; no such associations were found for internalizing or thought

problem dimensions". Combining this finding with the subjective perceptions reported after Cyberball conditions, this blunted physiological response could be expression of deficits in autonomic flexibility, or an inability for the patients to adapt appropriately to environmental challenges and behavioral demands, rather than indices of emotional regulation strategies (Andersen et al., 2019).

Considering together the blunted emotional and physiological response and the lack of behavioral activation facing ostracism could be expression of social cognitive deficit, defined as a cognitive capacity to represent and predict one's own and other persons' mental states in terms of thinking, believing, or pretending. This deficit has been observed in SCZ patients at an advanced stage of illness, at onset, and in their first degree relatives (Biedermann et al., 2012; Bora and Pantelis, 2013), configuring the hypothesis that it may be a endophenotype of the disease.

The altered ability to mentalize and to use this information to effectively deal with problematic situations, both from an emotional, cognitive and behavioral point of view, characterizes the world of SCZ patients and could affect their social dysfunction.

From a phenomenological perspective, our results support the clinical notion that patients with SCZ *"cut themselves off as much as possible from any contact with the external world",* because of a *"detachment from reality with the relative and absolute predominance of the inner life",* called autism (Bleuler, 1911). This detachment, according with Minkowski, is a deficit in the basic, non-reflective attunement between the person and his world, i.e., a *lack* of "vital contact with reality", defined as an ability to "resonate with the world", to empathize with others, an ability to become affected and to act suitably, as a pre-reflective immersion in the intersubjective world, which leads to the "crisis of common sense" or "loss of natural evidence" that have greater implication for social functioning (Blankenburg, 1971).

Of interest, no association was found between the positive or negative symptoms of SCZ and the perception of threat to fundamental need or the RSA reactivity in the condition of ostracism. This finding suggests that the specific vulnerability towards blunted response to social exclusion does

not depend on the clinical profile of the SCZ. This results support the view that although the autistic features are sometimes treated on a par with the so-called "negative symptoms", the experiential, subjectively perceived, anomalies do not necessarily lead to behavioral disorders, as measured by the PANSS negative subscale.

Regarding the limitation of the present study we reported that our results could be due to an erroneous perception of the Cyberball condition in patients with SCZ. Considering the manipulation check responses, that determine the validity of the experimental manipulation, SCZ patients reported to have received a higher number of throws in the Inclusion condition and stated that they were less excluded during Ostracism, compared with than HC. This finding could be related with the neurocognitive difficulties in working memory, attention, processing speed, visual and verbal learning, that have been extensively documented in SCZ (Heinrichs and Zakzanis, 1998). Therefore we cannot exclude that the blunted response to ostracism could be a consequence of general cognitive alterations rather than a specific impairments in social processing.

Moreover, in this study, patients were not excluded for regular psychopharmacological treatment, which included mainly antipsychotic and benzodiazepine. Therefore we cannot exclude that medications could have affected the parasympathetic tone at baseline. However, previous studies showed that antipsychotic medication did not change significantly the autonomic function (Malaspina et al., 2002, Bar et al., 2005, Boettger et al., 2006), although other author observed that some of these drugs suppressed HRV (Agelink et al., 2001; Cohen et al., 2001; Kim et al., 2004). Low RSA at baseline was measured also in patients with SCZ that were not taking any psychopharmacological therapy (Alvares et al., 2016) and in their first degree relatives (Castro et al., 2009; Jáuregui et al., 2011), suggesting that it is unlikely that this effect could be related only to medications. Moreover, Aguirre and colleagues (2018) found an autonomic improvement in response to antipsychotic treatment in an inpatient with SCZ in acute psychosis, suggesting that concurrent improvement of psychosis and autonomic function in response to antipsychotic treatment could be due to a potential cardio protective role of antipsychotics.

In conclusion, this study showed that also patients with SCZ present an autonomic vulnerability, with reduced vagal control at rest. Moreover, they reported blunted perception of threat and aggressive responses in condition of social exclusion, compared with HC, and maintained lower parasympathetic tone during the interpersonal exchange. These findings support the view that SCZ patients present a fundamental disposition to introversion and detachment, suggesting that these alterations are deeply rooted at the physiological level. Therefore, considering that patients with SCZ may benefit from specialized behavioral training programs to improve high- level social cognitive functioning (Biederman et al., 2012), intervention on perceiving subtle social cues when faced with social threat might be recommended.

V. Interoception and psychopathology: relevance for impairment in social interaction

V.a. Introduction

In recent years, there has been a surge of interest in interoception because of its impact on physical health (Quadt et al., 2018), mental health (Khalsa et al., 2018), as well as emotional functioning in general (Critchley and Garfinkel, 2017).

Interoception and Psychopathology

Among the studies that have linked dysfunctions of interoception to mental health conditions, two main approaches emerged: the categorical and the dimensional approach (Kalsha et al. 2018).

Following the categorical approach, previous research suggests an atypical interoception for different psychopathology, with 'atypical interoception' encompassing both atypically high or low interoceptive ability.

Regarding MDD a recent reviews (Eggart et al., 2019) reported heartbeat-related interoceptive impairments in MDD. The main findings suggest that differences between subjects with MDD and HC on a heartbeat mental tracking task performance depend on depression severity, suggesting a non-linear association between IA and depression severity (Dunn et al., 2007). These authors suggested an inverted U-shaped curvilinear relationship between depression severity and error rates on heartbeat task, resulting that moderately depressed samples exhibit the largest interoceptive deficits as compared with HC that seems to normalize in both euthymic and severely depressed subjects. The author emphasized, however, the effect of possible confounding factors, like the level of anxiety, which is often associated with depression and is commonly related with higher levels of IA, and the effect of SSRIs that has been suggested that possibly exert an IA increasing. To our knowledge (Avery et al., 2015), no studies determined if the abnormal interoceptive activity reflects a state or trait effect, by assessing MDD patients in the remitted condition of MDD.

Considering BPD, in a preliminary study Mussgay and colleagues (1999) observed that individuals with a personality disorder, with no differentiation between the heterogeneous types of personality

disorder, have deficits in their ability to perceive their heartbeat when compared to a functional cardiac group and the nonclinical comparison group. However, more recently, contrary with their hypothesis that individuals with a BPD would have poorer IA than a nonclinical comparison group (Bateman & Fonagy, 2005; Linehan, 1993), Hart and colleagues (2013) showed that there were no significant differences in the level of IA between BPD patients and nonclinical controls, in two interoceptive tasks, namely, the heartbeat perception task and the mental tracking task. Their findings provide strong evidence that IA is intact in BPD, contradicting the notion that difficulties in emotional regulation in BPD are connected to differences in IA and suggesting that the perception of physiological sensations, which can have an impact on emotional experiences, should not be a focus of therapeutic intervention. The neurophysiological evidence (Mueller et al., 2015) showed abnormal representation of interoceptive afferences in BPD: the amplitude of heart-beat-evoked potentials was negatively associated with emotional dysregulation and positively with gray matter volume in the anterior insula and the bilateral dorsal anterior cingulate cortex.

These findings of unaffected IA and impaired representation of interoceptive signals has been interpreted in line with Garfinkel and Critchley model that proposed that there are distinct and independent dimensions of interoception: while IA describes a comparatively low-level and objectifiable interoceptive performance, interoceptive awareness refers to a higher order metacognitive representation feeding on the association of interoceptive performance and confidence about one's interoceptive capabilities. Presumably the neurophysiological alteration in patients with BPD could be expression of altered interoceptive awareness, which is generalizable across different inner physiological process and negatively related to emotional responsiveness (Löffler et al., 2018).

Finally, among patients with SCZ, IA has been demonstrated significantly lower when compared to HC (Ardizzi et al., 2016). This finding has been interpreted as expression of an altered experience of the basic sense of self (i.e., body ownership and sense of agency), which may play a fundamental role in self-other distinction and has been proved to be related to interoception in healthy

participants (Palmer and Tsakiris, 2018). Moreover, according with these authors, there is a linear relation between IA and only positive symptoms of SCZ, in particular grandiosity, suggesting that positive symptoms, in particular grandiosity and grandiose delusions, might be protective against the altered basic sense of self characterizing patients with SCZ with higher sensibility to inner bodily sensations.

Interoceptive dysfunction also likely plays a role in conditions such as eating disorders, drug addiction, posttraumatic stress disorder and somatic symptom disorders, tic disorders, autism spectrum disorder and obsessive-compulsive disorder (Khalsa et al., 2018). Therefore, based on evidence of interoceptive difficulties in a broad range of psychiatric conditions, many authors recommended studying interoception using a dimensional approach, suggesting that interoceptive processes are not readily identified at the symptom level and did not have entered into the diagnostic classifications, but might constitutes the p-factor accounting for symptom commonalities between psychiatric disorders (Brewer et al., 2016). This approach could bridge the biological gap in current diagnostic classification frameworks by directly probing the links between physiological and psychological dysfunctions.

In particular, a recent paper (Murphy et al., 2016), using a trans-diagnostic perspective, suggests that poor IA is typical in individuals with high levels of alexithymia. This view is supported by research associating the anterior insula, the brain area in which interoceptive signals concerning the state of the body converge, with alexithymia. Alexithymia is a sub-clinical condition, which has traditionally been defined in terms of difficulties identifying and describing one's own emotions (Nemiah et al., 1976), but recent evidence suggests that alexithymia may be characterized by atypical interoception, rather than with specific difficulties in the affective domain (Brewer et al., 2016).

In fact interoception provides a perception of inner movements ('feeling of feelings'): the basis for the emotional awareness and representation of the body from within (Damasio and Carvalho, 2013). Therefore it is assumed that interoception is not only involved in emotional attunement to the

environment, but also in distinction between one's own and the others' emotions. Distinction and attunement between self and others enable engagement in social interactions.

Considering the diagnostic group included in this study, previous research suggested that in MDD alexithymia is a state-dependent phenomenon related with depression (Marchesi et al., 2008). Marchesi et al. (2000) showed that, although alexithymia and depression are separate constructs, they are closely related. In fact, alexithymia in depressed patients seems to be the result of a parallel change between symptom severity and Toronto Alexithymia Scale score, which increase and decrease together, suggesting that alexithymia may be a temporary response to stress represented by a depressive episode (Lumley, 2000).

Our group of research also focused on the nature of the alexithymic difficulties eventually endorsed by personality disorders patients. De Panfilis and colleagues (2015) showed that personality disorders in general are not invariably associated, per se, with alexithymia. Rather, difficulties in identifying and communicating emotions are likely to be fostered by their comorbid psychiatric symptom severity. In fact alexithymia is specifically associated with personality disorders at low levels of psychopathology, suggesting that for patients with severe psychological distress alexithymic difficulties are mainly fostered by their non-PD symptom burden. In that study, in particular, BPD was not associated with difficulty identifying feelings suggesting, in line with Hart et al. (2013), which showed, using a heart beat task, that deficits in labeling the physiological sensations of emotions do not represent specific markers of BPD.

By contrast, heightened levels of alexithymia were found in a number of different schizophrenia samples (Stanghellini and Ricca, 1995, Cedro et al., 2001, Todarello et al., 2005, Van't Wout et al., 2007, van der Meer et al., 2009, Koelkebeck et al., 2010, Kubota et al., 2011). These findings have led to hypothesize that alexithymia may be a personological prerequisite for developing a negative syndrome (Stanghellini and Ricca, 1995), a vulnerability factor for the development of schizophrenia (Van't Wout et al., 2007, van der Meer et al., 2009), and may be an underlying cause of social dysfunction in patients with SCZ. However other authors suggested alexithymia in SCZ is

more heterogeneous and has several components, some of which are more state-related, and others of which are more like trait features (Maggini and Raballo, 2004). Moreover alexithymia may not be affected specifically in SCZ, but SCZ-related difficulties do emerge in contexts where cognitive demands are incremented, like in performance-based measures of this construct (Henry et al. 2010).

The role of interoception in social behavior

Recent evidence suggests that interoception are bi-directionally related to higher-order psychological functions such as self, emotions and social processing (Loeffer et al., 2018). Dysfunctional social information processing may account in part for the reduced overall social functioning in psychopathology.

In particular there are several studies suggesting an intriguing link between interoception and social reactivity. Werner and colleagues used a public speaking stress test (2009) and a social exclusion task in a conversation with confederates (2013), showing that people higher in IA reported less negative affect after the challenging social situation, despite their physiological reactivity being comparable to participants with lower IA. Another study induced social exclusion with the Cyberball game and similarly found that higher IA was associated with less negative affect as well as behavioral affiliation tendency, as measured by preferred interpersonal distance (Pollatos et al., 2015). By contrast, null results on the effect of IA buffering against negative affect from Cyberball were found in a recent study conducted by Zamariola et al. (2019).

Although not directly manipulating social interaction, another study showed how IA relates to peripersonal space – the region just surrounding one's body in which multisensory integration is heightened for salient processing (Ferri et al., 2013). This study showed that the higher IA is associated with greater RSA reactivity, one of the periodic components of heart rate variability in response to seeing another person's hand entering their peripersonal space (i.e., 20 cm from their own hand). Critically, this result was not seen when the entering object is a metal stick. Given that an approaching human hand is a proxy for social connection, this result is consistent with the possibility that interoception facilitates noticing of a potential social connection. On the contrary,

participants with low IA showed autonomic activation only when other's hand occupied their personal space (0 cm from the participant's dominant hand), so when their hand was actually touched. In view of all this evidence, it is demonstrated that IA strongly influences human social behavior among healthy participants (Arnold et al., 2019).

The first aim of this exploratory study is to examine, trans diagnostically, whether SCZ, BPD and rMDD are associated with 'atypical interoception', compared with HC. Based on the aforementioned evidences we hypothesized that IA would be mostly reduced in patients with SCZ and could be expression of their reduced tendency to focus on inner experience and, consequently, of impaired emotional attunement to the environment.

Secondarily, we aim to explore whether IA affects the emotional and physiological response to ostracism in a Cyberball paradigm, hypothesizing that IA would be a protective factor against the social stressors, as social exclusion.

V.b. Method

Participants

This study involved 130 participants: 30 patients with Borderline Personality Disorder (BPD), 30 patients with remitted Major Depressive Disorder (rMDD), 30 patients with Schizophrenia (SCZ) and 40 Healthy Controls (HC).

Patients seeking treatment at the outpatient Mental Health Unit of Parma, from January 2016 to September 2019, were included in the study. HC were recruited through advertisements in meeting places in the local community and among the personal staff of the University Hospital.

The clinical participants were recruited in a stable clinical phase and were on stable treatment with psychotropic drugs.

Inclusion criteria and exclusion criteria are detailed in the **General methods** (**Session IIa)**.

Measures and procedure

Psychometric assessment and experimental procedure for measure interoception were detailed in the **General methods (Session IIb and IIc)**.

Statistical analysis

After checking the normality and heteroscedasticity of the variables descriptive statistics were performed to detail socio-demographic and clinical characteristics of the sample.

To examine between groups differences in IA a one-way ANOVA was performed, entering IA as dependent variable and Group (BPD, rMDD, SCZ and HC) as the between-subjects factor. Bonferroni t-test was planned to explore any group effect.

Then in order to explore the effect of variables known to affect IA, which are different between groups, an ANCOVA was conducted, adding age, sex and Body Mass Index as covariates for the physiological measure.

Finally, splitting the sample based on the diagnostic group, exploratory bivariate associations between IA scores and emotional (NTS) and physiological (RSA reactivity) measures during the Cyberball game were reported using the classic Pearson's r coefficient of linear correlation.

For patients with SCZ, we also performed liner correlations between IA and the clinical symptoms of the PANSS.

All the analyses were carried out using SPSS software (IBM SPSS 25.0).

V.c. Results

Sample

The four groups (30 BPD, 30 rMDD, 30 SCZ and 40 HC) differed in gender, age and Body Mass Index (BMI) distribution. The socio-demographic and clinical characteristics of the participants are presented in **Table 5**.

Table 5. Socio-demographic and psychometric characteristics of the sample

	HC	rMMD	BPD	SCZ	Between-groups differences	
	n= 40	n=30	n=30	n=30	Main effect of factor Group	Post-hoc comparisons
Age	38.7±13.66	49.27±9.96	33.27±12.12	38.17±10.49	$F_{(3,129)}$=9.77, p< .01; μ^2_p=.18	rMDD> HC>SCZ>BPD (p_s<.01)
Sex (F)	23 (57.5%)	26 (86.7%)	27 (90%)	8 (26.7%)	χ^2 (3)= 34.61, p<.01	
Education (yrs)	15.27±3.44	11.23±3.35	11.53±2.89	10.43±3.38	H (3)= 34.03, p< .01	HC>BPD, rMDD, SCZ (p_s<.01)
Matrix reasoning	20.70±2.99	18.16±3.38	16.80±2.42	17.23±3.72	$H(3)_{)}$= 27.662, p< .01	HC>BPD, rMDD, SCZ (p_s<.07)
BMI	23.43±3.44	26.31±6.25	21.77±3.75	27.08±5.58	$H(3)_{)}$= 20.54, p< .01	rMDD, SCZ> BPD, HC (p_s<.01)
Psychotropic drugs consumption						
Alcohol	27 (67.5%)	7 (23.3%)	15 (50%)	13 (43.3%)	χ^2 (3)= 13.71, p<.01	
Caffeine	35 (87.5%)	19 (63.3%)	24 (80%)	16 (53.3%)	χ^2 (3)= 12.09, p<.01	
Tobacco	10 (25%)	5 (16.7 %)	24 (80%)	10(33.3%)	χ^2 (3)= 31.49, p< .01	
Family status						
Married/living together	20 (48.5%)	20 (66.6%)	7 (23.3%)	2 (6.6%)		
Separated/divorced	1 (3.3%)	4 (13.4%)	6 (20%)	0 (0%)	χ^2 (6)= 47.69, p< .01	
Widowed	1 (3.3%)	1 (3.3%)	0 (0%)	0 (0%)		
Living alone/with parents	16 (40%)	5 (16.7%)	17 (56.7%)	26 (86.7%)		
Occupation						
Employed	25 (60%)	22 (73.3%)	16 (53.3%)	13 (27.9%)		
Housewife	4 (13.3%)	6 (20%)	0 (0%)	0 (0%)	χ^2 (6)= 51.73, p< .01	
Students	11 (27.5%)	0 (0%)	6 (20%)	2 (6.7%)		
Unemployed	1 (2.5%)	2 (6.7%)	8 (26.7%)	15 (11.5%)		
GAF	97.32±4.64	86.57±6.39	72.07±7.31	61.16±13.06	H(3)= 102.94 (p<.01)	HC>rMDD>BPD>SCZ(p_s< .01)

HC: Healthy Control, rMDD: remitted Major Depressive Disorder, BPD: Borderline Personality Disorder, SCZ: Schizophrenia, BMI = Body Mass Index GAF = Global Assessment of Functioning, H= Kruskal–Wallis H test, *χ2* = Pearson's chi-squared test

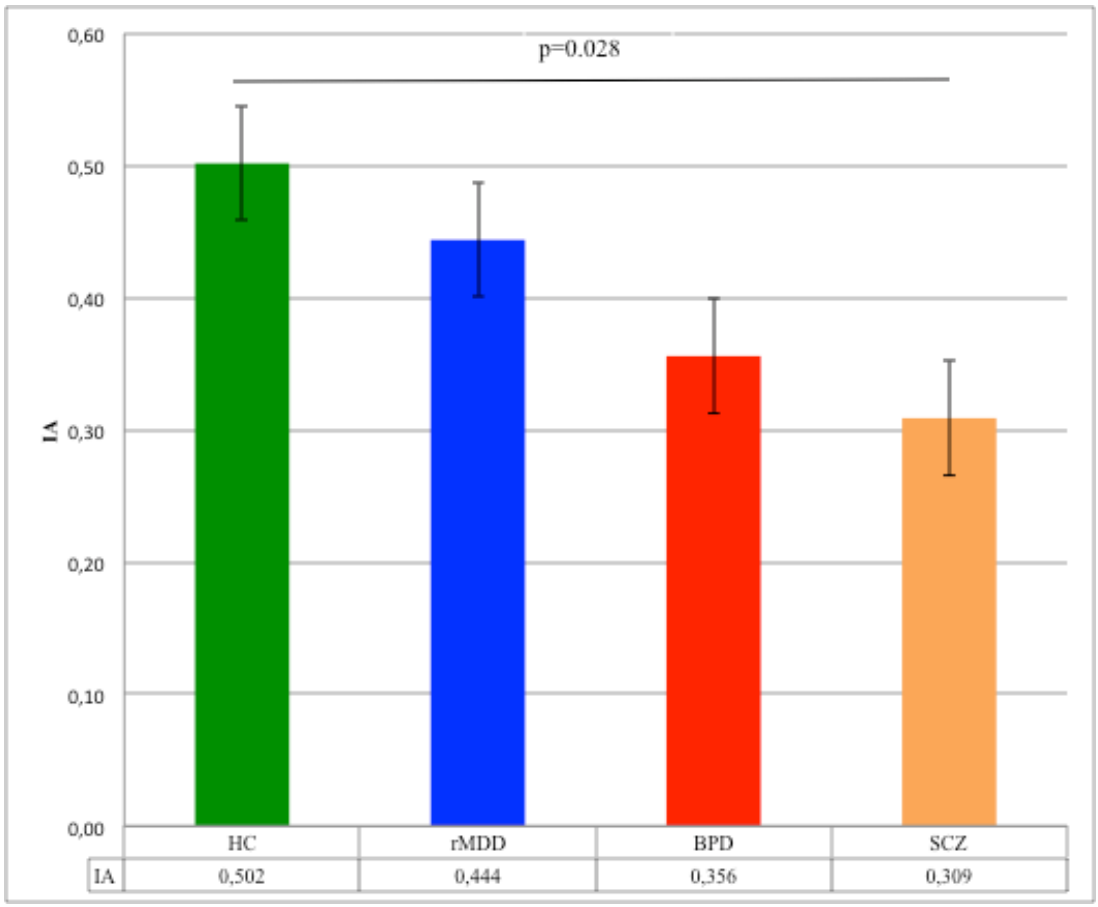
IA

Group differences were observed for IA at baseline (F1.129=3.30, p=0.023), even after controlling for age, sex and BMI (F2.129=3.529, p=0.017).

At direct comparison both patients with BPD (p=0.05) and SCZ (p=0.05) presented reduced IA compared with HC.

However, adding the covariates that could affect IA, the post-hoc comparisons revealed that only patients with SCZ presented a significant lower IA compared to HC (p=0.028, CI=-0.373, -0.013) while the mean IA for BPD, rMDD and SCZ patients did not differ from HC (**Figure 6**).

Figure 6. Interoceptive Accuracy (IA) marginal means for HC, rMDD, BPD and SCZ participants.



HC: Healthy Control; BPD: patients with Borderline Personality Disorder; SCZ: patients with Schizophrenia; rMDD: patients with remitted Major Depressive Disorder

IA and responses to social exclusion

Exploratory correlations between IA and rNTS score and RSA reactivity, respectively, were reported in **Table 6**.

Table 6. Correlations between IA and emotional and physiological response in different diagnostic groups

IA	HC	rMDD	BPD	SCZ
1. rNTS inclusion	r=-1.73 p=0.28	r=-0.19 p=0.30	**r=-0.364** **p=0.04***	r=-0.02 p=0.89
2. rNTS ostracism	r=-0.25 p=0.12	r=-0.04 p=0.81	r=-0.09 p=0.61	r=-0.27 p=0.15
3. RSA reactivity inclusion	r=-0.23 p=0.15	r=-0.11 p=0.55	r=0.19 p=0.30	r=-0.12 p=0.15
4. RSA reactivity ostracism	r=-0.03 p=0.83	r=-0.04 p=0.82	r=0.23 p=0.22	**r=-0.40** **p=0.03***

rNTS: reversed Need Threat Scale, RSA Respiratory Sinus Arrhythmia HC: Healthy Control; BPD: patients with Borderline Personality Disorder; SCZ: patients with Schizophrenia; rMDD: patients with remitted Major Depressive Disorder

We did not find any significant correlations between IA and emotional and physiological responses in the samples of HC and rMDD.

Among patients with BPD, we found a significant negative correlation between IA and rNTS during inclusion, showing that patients with higher IA present a reduce sense of threat to human fundamental needs in the condition of inclusion.

Regarding patients with SCZ significant negative correlation was observed between IA and rNTS during ostracism, indicating that patients with higher IA reported less subjective perception of threat, compared with patients with lower IA. However, by contrast, they presented significantly lower RSA reactivity level during ostracism, which is considered expression of a physiological perception of threat.

IA and symptoms of schizophrenia

We observed a significant negative correlation between IA and 2 items of PANSS scale, related with negative symptomatology and experiential deficit: Blunted affect (N1: r=-0.437 p=0.026) and Active Social Avoidance (G16: r=-434 p=0.027).

V.d. Discussion

The results of this study showed that IA is not a-specifically altered among psychopathology, but it is possible to identify associations between IA and diagnostic subtypes. We found that patients with SCZ and BPD displayed both significantly lower IA when compared to HC. However, for patients with BPD, this difference seems to be explained by participants' differences in sex, age or BMI.

Regarding SCZ our finding replicated previous evidence (Ardizzi et al., 2016) suggesting that impairment in IA represent a stable trait feature for this disorder. IA assumes a fundamental self experience related to the implicit and pre-reflective notion of the self (Tsakiris et al., 2005). Past work by Damasio (1999) argues that constant transmission of signals, which reflect the body's internal states, is necessary for the construction of selfhood and ultimately consciousness. Anomalous subjective experiences indicative of some sort of disturbance of instability in the basic sense of self have been identified in schizophrenia spectrum conditions (Nelson and Sass, 2017). In particular experiential distance emerges between the self and bodily experience: one no longer "inhabits" one's body and therefore present problems in attribute internal body sensations to one's self. The experience of being a self signifies that we live our (conscious) life in the first-person perspective, as a self-present, single, temporally persistent, bodily and bounded subject of experience and action. Therefore we interpreted this finding as expression of 'disordered self', constituting a trait feature of SCZ, related with the core of this disorder.

Considering BPD, our results confirmed that IA overall is intact in BPD (Hart et al., 2013). This suggests that difficulties in identifying internal body signals, as difficulties in identifying and communicating emotions, are not invariably associated with BPD (De Panfilis et al., 2015), but other factors, like the level of psychopathology and higher order capacities, could impact on physiological and emotional awareness. In fact, as previously reported, this result could not exclude interoceptive difficulties among patients with BPD. A recent model (Löffler et al., 2018) proposed interoception as an important connecting variable that could be associated with reduced emotional awareness, which in turn mediates the relationship between adverse (early) life experiences and

emotion regulation deficits in adulthood. According with these authors the dimension of IA describes a comparatively low-level and objective interoceptive performance, which could differ from interoceptive awareness, a higher order metacognitive representation of bodily sensations.

Finally, considering again the comparisons between groups, we found that patients with MDD, in remission phase, did not differ form HC, representing a valid clinical control group also for this physiological measure. To our knowledge no previous study assessed IA in sample of MDD patients in phase of remission. However, according with a recent review (Eggart et al., 2019), differences in IA between subjects with MDD and HC on a heartbeat mental tracking task, seem to depend on depression severity, in line with the evidence of a state- dependent alexhythimia in MDD. An alternative explanation could be related with the effect of anxiety: clinical and subclinical levels of anxiety were associated with increased IA (Domschke et al., 2010). Since depressive and anxiety symptoms occur concomitantly in most patients with MDD, the decreased accuracy of depression could be masked by subclinical level of anxiety.

Focusing on the association between IA and social responses in the Cyberball game, the exploratory analysis here reported highlights the relevance of the perception of bodily signals for emotional and physiological responses to ostracism, in psychopathology.

We did not find any significant correlation between IA and emotional or physiological responses to Cyberball, in HC and patients with rMDD. Among patients with BPD we observed a significant negative correlation between IA and rNTS in the inclusion phase. While, in the group of patients with SCZ, we observed a significant negative correlation between IA and RSA reactivity during ostracism, and a significant negative correlations between IA and clinical symptoms of the PANSS scale, expression of negative symptomatology and experiential deficit in social contexts.

In line with the findings of Zamariola and colleagues (2019), conducted on a large sample (n=534) of healthy subjects, our results did not confirmed that higher interoceptive abilities help people to cope with the negative emotional consequences of adverse circumstances, as previously demonstrated by Werner et al. (2013) and Pollatos et al. (2015). The lack of support for the

‘regulation advantage hypothesis’ could be attributed to then fact that heightened IA is associated with trait anxiety (Pollatos et al., 2007; Domschke et al., 2010), which in turn is associated with reduced emotion regulation capacity (Suveg and Zeman, 2004). More anxious individuals are more aware of their heartbeat, therefore, it might be that the relationship between interoception and emotion regulation follows a reverse U-shaped function, up to the point that paying too much attention to bodily signals may predict disordered emotion recognition and regulation. This view was recently supported in a study in which the relationship between interoceptive sensibility and anxiety was mediated by alexithymia: individuals with anxiety trait reported both greater interoceptive sensibility and higher alexithymia (Palser et al., 2018). Another possible explanation for our negative finding could be the limited sample size of our control group, that did not allow selecting patients extremes values of high versus low interoception, with one standard deviation above and below the mean IA score, as reported by Pollatos and colleagues (2015).

In the first study of this dissertation we found that patients with BPD reported significant perception of threat during the fair inclusive condition, compared with HC. Here we found that the participants with BPD with higher IA reported less feelings of threat, during the including interaction, compared with lower IA participants. This suggests that an intact interoception might represent a protective factor in BPD, that allows feeling safe in social exchanges, buffering against the rejection sensitivity dynamics.

Consistently, in the second study that we presented in this dissertation, we observed that SCZ is associated with a blunted emotional and physiological response. Again, among patients with SCZ, IA might allow identifying a subgroup of patients, with higher IA, that display a physiological response to social exclusion (RSA withdrawal during ostracism). Moreover these SCZ patients with higher IA reported reduced blunted affect and greater ability to engage in social relations, at the clinicians’ evaluation. Therefore these preliminary findings could led to the interesting idea that perhaps greater IA allows SCZ patients to objectively identify the feelings induced by the external

“social situation”, rather than to attribute these feelings to the self, inducing a proper physiological response, that could reflect better emotional regulation in challenging situation.

These findings, however, should be interpreted with caution considering that the main limitation of this study is the lack of validity of the interoceptive measure used here and in previous research. The heartbeat counting task, the measure that represents the gold standard for interoceptive accuracy assessment, has been questioned by various authors who argued that people performing this task may rely on prior semantic knowledge about heart rate instead of attempting to perceive them (Desmedt et al., 2018; Ring et al., 2015; Zamariola et al. 2018).

Moreover splitting the sample in clinical diagnostic group, the results could be affected by the sample size and the significant correlations that we found could be the result of chance factors, although they appeared coherent with previous findings.

In conclusion we investigated trans-diagnostically IA in different form of psychopathology and we found that patients with SCZ showed a severe failure in the ability to detect internal bodily signals, that might depend on their disturbed basic self experiences. Furthermore IA was inversely associated to the dysfunctional emotional and physiological responses to social interactions in SCZ and BPD patients, suggesting that interoception could be a potential mediator for patients' difficulties in challenging interpersonal situation.

VI. General discussion and conclusions

The present dissertation focuses on the role of autonomic control on social behavior, across psychiatric disorders, in which compromised social functioning is a diagnostic feature, e.g. Borderline Personality Disorder (BPD) and Schizophrenia (SCZ). Whereas in the former the impairment in social functioning reflects a disturbed psychological self-organization, in the latter it seems to be most related with deficit syndrome symptoms. A group of patients with Major Depressive Disorder in phase of remission (rMDD) was recruited as clinical control group, as well as a group of Healthy Control (HC).

Among these disorders we investigated how autonomic control is related with emotional perceptions in response to an experimental condition of social exclusion.

Social exclusion in fact is a major psychosocial factor contributing to the development and persistence of psychiatric disorders and is also related to their social stigma (Reinhard et al., 2019). Specifically, we studied the experience of ostracism, which is defined as being ignored and/or excluded by others (Riva et al., 2016). According to the Temporal Need-Threat Model developed by Williams (William et al., 2009), in our studies the effect of ostracism was examined across distinct phases. The "reflexive stage" is the first stage, when rejection is detected, and it is felt that the four basic needs (belonging, self-esteem, control and meaningful existence) are not satisfied, as a result of which negative mood is put forth together with physical and social pain. The "reflective stage" is the second stage of the rejection process, when the individual focuses all his/her attention to the process of rejection in order to be able to cope with the negative effects of being ostracized.

Psychiatric symptoms increase the chance of being ostracized and ostracism consolidates or even aggravates psychopathology, suggesting the overall concept of a vicious cycle. Among patients with psychiatric disorders chronic social exclusion might persistently threaten the fundamental psychological needs, inducing the third chronic stage of ostracism, called the "resignation stage".

Considering the ability to cope with ostracism as a fundamental social skill driving also the subsequent behavioral responses, we investigated how the Autonomic Nervous System, and

especially the vagal regulation responses, could represent a valid measure of individuals' ability to self-regulate in social contexts (Porges et al., 1994/2011).

The vagal activity at rest, which can be indirectly estimated by means RSA recording (Berntson et al., 1993), has been proposed to be a an autonomic, transdiagnostic biomarker of mental illness, representing a measure of humans' ability to establish a physiological state suitable for social relations (Porges, 2003; 2007; Porges et al., 2011).

The association between the vagal modulation (RSA reactivity) to environmental social stimuli and psychopathology was considered more complex: the ability to adapt autonomic responses, in order to cope with social environmental stimuli, has been considered a great advantage for social functioning. We focused therefore on psychiatric disorders (BPD and SCZ) characterized by social functioning impairment, in which emotional dysregulation and compromised social behaviors are diagnostic features, to test whether their specific psychopathologies are associated with autonomic regulation strategies that foster defensive and not social behaviors.

The degree of social inclusion or ostracism was manipulated using Cyberball, a virtual ball-tossing game that is widely used in social psychological experiments. In this game the participant supposedly plays with two other participants, who are in fact part of the computer program. Following the classical version of the game, participants played two consecutive games, inclusion and ostracism. During Inclusion, players are repeatedly passed the ball and obtain an equal number of ball tosses as the other players. During Ostracism, players are not passed the ball after two initial tosses. A recent meta-analysis showed that at least 200 published papers involved the use of the Cyberball paradigm to study ostracism and that over 19,500 participants have played the game thus far (Hartgerink et al., 2015).

A second consideration guided the present dissertation. To date most researches focused on interoceptive accuracy (IA) - performance on objective behavioural tests of heartbeat detection - demonstrating its influence not only on human cognition (Werner et al., 2009), but also on human social functioning (Tsakiris and Critchley, 2016). Recent findings, using heartbeat perception tasks,

showed that IA is positively associated with greater intensity of emotional experience (Herbert et al., 2011) and greater activation of anterior insular cortex, that has been shown to be of relevance for interoception (Critchley et al., 2004; Pollatos et., 2007) and the representation and integration of interoceptive bodily signals with higher order and emotional processes (Craig, 2002, 2009). We investigated the presence of deficit in representation of internal bodily signals, among the psychiatric disorders that we included in our study, speculating a possible association with alexithymia, a personality construct that is characterized by marked deficits in the abilities to identify and describe one's feeling. Moreover, in line with a previous study (Ferri et al., 2016), we evaluated IA influences on social behavior, using both explicit and autonomic measures. Therefore preliminary analyses were conducted to explore potential associations between interoception, emotions and autonomic regulation, in BPD, SCZ and rMDD, during social exclusion.

Bearing in mind these two opening considerations, in the present dissertation we reported three successive experiments.

In the first experiment were involved 30 patients with BPD, 30 patients with remitted Major Depression (rMDD) and 30 healthy controls (HC). In BPD, social impairment is fostered by a unique pattern of interpersonal hypersensitivity, encompassing extensive preoccupation with real or imagined abandonment and rejection and related distrustful perceptions of others as bad, malevolent, and excluding (Gunderson, 2010; Clarkin et al., 2006). Using the Cyberball experiment, we investigated whether patients with BPD feel rejected even when socially included by others (rejection bias) and whether they display a peculiar pattern of changes in Respiratory Sinus Arrhythmia (RSA), index of social flexibility, after the conditions of social inclusion and ostracism. The results showed that before the task, BPD presented reduced tonic RSA as compared with HC, indicating stable difficulties in social predisposition. After the Cyberball Inclusion condition, BPD self-reported greater threats to fundamental needs than non-BPD controls; moreover, only in BPD threats to fundamental needs did not decrease from ostracism to the reflective stage. Further, at the reflective stage BPD reported higher rejection-related emotions than

non-BPD controls. Finally, only among BPD patients RSA decreased during the game as compared to baseline, regardless of the experimental condition.

Thus, we found that patients with BPD show a physiological bias to feel vulnerable during social interactions, which make them respond with greater physiological arousal to any social situation, and with greater feelings of ostracism after actually benign social scenarios, i.e., following social inclusion and when the ostracism experience is over.

For the second experiment we recruited 30 patients with SCZ and 30 matched HC. Negative symptoms, cognitive deficits and impairment of social cognition are the SCZ-related variables mainly associated to poor functional outcome, that have been proposed to underlie the *schizophrenic autism*, defined as disturbance of the self-world relation that includes detachment from outer reality associated with a predominance of an "inner life" (Stanghellini et al., 2017). We run the experimental paradigm, using the Cyberball task, assessing whether patients with SCZ report blunted emotional and autonomic responses to ostracism, suggesting that they would not adequately perceive and deal with potential social threats.

The results showed that patients with SCZ displayed a reduced cardiac vagal tone at baseline, considered an unspecific index of difficulties in social predisposition. Moreover, subjectively, they perceived fewer threats to the human fundamental needs and did not develop aggressive tendencies, in response to ostracism, compared with the non-clinical participants. At the autonomic level no modulation was found during the interpersonal exchange.

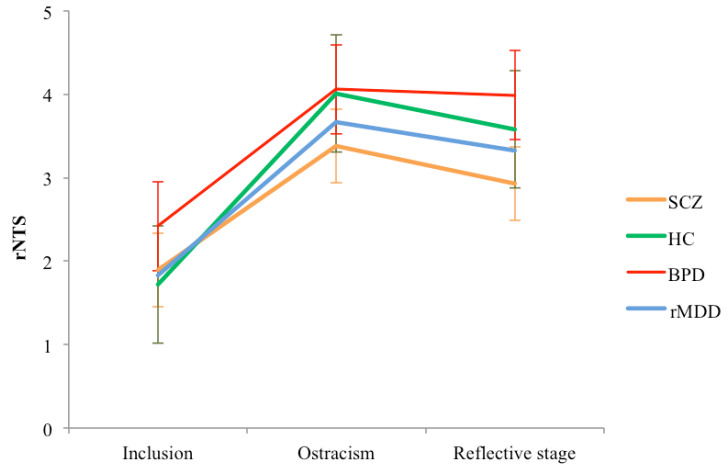
These findings confirmed clinical observations regarding a fundamental disposition to introversion and detachment in patients with SCZ, suggesting that these alterations are deeply rooted at the physiological level.

Considering together this experiments our results showed that the rejection sensitivity dynamics in patients with BPD determined greater perceptions of threat during inclusion and a state of physiological arousal during the whole social interaction. By contrast, among patients with SCZ, the deficit symptoms blunted the expected adaptive emotional responses to ostracism, that let us to

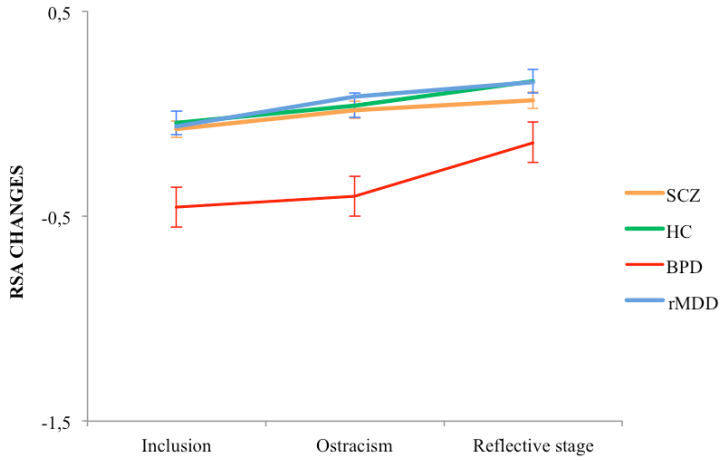
interpret the physiological results as a lack of modulation of vagal system, instead of a form of self-regulation, observed in HC (**Figure 7**).

Figure 7. Means for reversed Need Threat Scale (rNTS) scores (**Panel A**) and Respiratory Sinus Arrhythmia (RSA) changes (**Panel B**) across test conditions.

A.



B.



Finally, the third chapter of this dissertation focused on interoception. We compared Interoceptive Accuracy (IA), trans-diagnostically, in the three groups of patients (rMDD, BPD and SCZ) and in HC. Patients with SCZ displayed significantly lower IA when compared to HC, while IA overall is intact in BPD and rMDD. Problems in attribute internal body sensations to one's self has been interpreted as expression of the 'disordered self', related with the core of SCZ. Moreover, exploratory analyses revealed that IA could be linked the responses to ostracism, suggesting that altered interoceptive processes could be a potential mediator in psychosocial difficulties of patients

with BPD and SCZ. Further research should clarify whether specific psychopathological variables could explain such interoceptive difficulties.

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