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Neurophysiological correlates of reward processing and cognitive control in Borderline Personality Disorder patients with and without self-harm history

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Al meu avi.
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INDEX

List of Acronyms

ACC	Anterior Cingulate Cortex
BA	Brodmann's Area
BPD	Borderline Personality Disorder
DIB-R	Diagnostic Interview for Borderlines-Revised
DLPFC	Dorsolateral Prefrontal Cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
EF	Executive Functions
ERN	Error Related Negativity
ERP	Event Related Potentials
fMRI	Functional Magnetic Resonance Imaging
FRN	Feedback-Related Negativity
HC	Healthy Control
NI-BPD	BPD patients without non-suicidal self-injury behaviours
NSSI	Non-suicidal self-injury behaviours
OFC	Orbitofrontal Cortex
Pe	Error Positivity
PET	Positron-Emission Tomography
PFC	Prefrontal Cortex
SI-BPD	BPD patients with non-suicidal self-injury behaviours

Preface

Since their introduction in the *Diagnostic and Statistical Manual of Mental Disorders 3th edition* (DSM-III) in 1980, Borderline Personality Disorder (BPD) has received great interest from mental health clinicians and researchers. Patients suffering from BPD are often angry, impulsive and self-destructive. They present severe identity disturbances, fear of abandonment, brief psychotic episodes, problems with stress management and, consequently, show significant difficulties in their day to day functioning. Despite their clinical heterogeneity, strong alterations on affect regulation have been considered the most prominent clinical characteristic of these patients. In this scenario, turbulency is common as well as the presence of non-suicidal self-injury behaviours (NSSI). These kinds of behaviours have been associated with an increased likelihood of suicide in these patients. Current views in cognitive neuroscience have allowed a better understanding of high level cognitive functions which determine our adaptation to our environment, such as emotional self-regulation, decision-making, planning or learning. The application of this knowledge to the study of mechanisms underlying BPD (and NSSI behaviours) poses an interesting challenge in clinical research.

The following dissertation is devoted to the study of reward processing and cognitive control mechanisms in BPD patients. In particular, this dissertation aims to examine possible alterations in these higher order cognitive functions by using neuropshysiological (functional MRI and Event Related Potentials) and psychometric techniques, in order to reach a better understanding of the BPD phenomenology, and most concretely, of NSSI behaviours.

In *Chapter 1* of this thesis, an introduction to the main aspects and topics covered in the dissertation and in relation to BPD (NSSI behaviours, the reward system and cognitive control) will be provided. Special emphasis is given on neuroimaging research. *Chapter 2* describes two experiments on reward processing. The first one analyzes two specific reward-related ERP components in a sample of eighteen BPD patients and eighteen healthy controls. The second one is an fMRI study in which brain reward areas are investigated in a large sample of forty BPD patients (grouped in function of the presence of NSSI behaviours) and twenty healthy controls. *Chapter 3* describes two experiments of cognitive control in BPD patients. First, an ERP study in which the error processing is analyzed in a group of thirty-four BPD patients (grouped in function of the presence of NSSI behaviors) and seventeen healthy controls. On the other hand, in the second study the metacognitive capacity is assessed in a large sample of thirty-six BPD subjects and the corresponding thirty-six healthy subjects. The final chapter offers a summary of the experimental results and an integrative discussion.

Chapter I: Introduction

1. The Borderline Personality Disorder

1.1. Definition and main characteristics

The Borderline Personality Disorder (BPD) is a complex and serious mental disorder with a characteristic pervasive pattern of instability on affect regulation, impulse control, interpersonal relationships and self-image (Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004). It is a relatively new problem, inasmuch as, although the earlier definition of 'borderline personality' was made by Stern in 1938 (Stern, 1938), it was not until 1978 when Gunderson and Kolp (Gunderson & Kolb, 1978) established the contemporary definition. It appeared for the first time in the DSM-III (American Psychiatric Association, 1987) as a psychopathological entity and, since then, has certainly been the most studied personality disorder (see Figure 1).

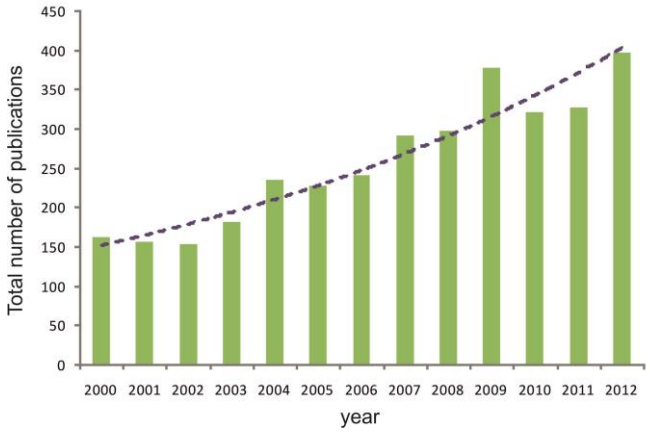


Figure 1. Total number of publications containing the term 'borderline personality disorder' according to MedLine database, from 2000 to 2012. The line shows the exponential increase of the number of publications.

Recently, with the arrival of the DSM-5 (American Psychiatric Association, 2013), it has suffered important changes in its conceptualization, because two different options for their diagnostics (categorical and dimensional; section II and III) have been included. Table 1 shows the main differences between the new dimensional DSM-5 criteria in respect to the categorical DMS-IV-TR ones (American Psychiatric Association, 2000).

Changes in the new DSM have generated a vigorous debate since it was presented on 18 May in San Francisco at the start of the American Psychiatric Association 166th annual meeting. Since then to the present day (approximately 10 months), numerous publications have emerged in their favour and, also, against it (*e.g.,* Carroll, 2013; Casey et al., 2013; Kendler, 2013; Regier, Kuhl, & Kupfer, 2013; Skodol, Bender, & Morey, 2013). The controversy has been not only from within the psychiatric community but also from outside them. Thus, for example, the president of the National Institute of Mental Health (N.I.M.H.), Thomas Insel, strongly criticized the DSM new version in the The New York Times, arguing that their categories lacked validity and were not based on any objective measure adding that 'people think that everything has to match D.S.M. criteria, but you know what? Biology never read that book' (Belluck & Carey, 2013). Not everyone is in agreement with these statements, as demonstrated a post edited by The New Yorker entitled 'the rats of N.I.M.H' in response to Insel (Greenberg, 2013). No doubt, this controversy is due, at least in part, to the potential implications of the changes in the DSM-5 as stated in a The New York Times opinion paper: 'So why the fuss over D.S.M.-5? Because of the unwarranted clout that its diagnoses carry with the rest of society: They are the passports to insurance coverage, the keys to special educational and behavioral services in school and the tickets to disability benefits' (Satel, 2013).

Prevalence. The BPD affects approximately 1-2% of the general population (Coid, Yang, Tyrer, Roberts, & Ullrich, 2006; Torgersen, Kringlen, & Cramer, 2001) and 15-25% of the clinical population (McGlashan et al., 2000). Despite traditionally being assumed that it is three times more common in women than in men (Skodol & Bender, 2003), the most recent studies suggest that lifetime prevalence in the general population is very similar in men (5.6%) and women (6.2%) (Grant et al., 2008).

Lamentably, the epidemiological studies in own society have been scarce and the data is inconclusive. One example is a recent study that analyzed the clinical history of 4.764.729 individuals in Catalonian primary care services, which found a detected prevalence for BPD of only .017% (Aragonès, Salvador-Carulla, López-Muntaner, Ferrer, & Piñol, 2013).

Comorbidity. Because BPD is very heterogeneous its symptoms overlap considerably with other conditions (*e.g.* depression, anxiety) (Paris, 2007), showing high presence of co-morbidity and a low frequency of 'pure' BPD (occurring only in 3-10% of cases) (Pfohl, Coryell, Zimmerman, & Stangl, 1986). In consequence, around 84% of BPD patients met the criteria for one or more twelve-month axis I disorders, and 75% met the criteria for co-morbid lifetime axis II disorder (Grant et al., 2008). Especially, those most comorbid are the DSM-IV cluster B personality disorders (histrionic, narcissistic and antisocial) as well as mood and anxiety disorders (McGlashan et al., 2000; Oldham et al., 1995; Tyrer, Gunderson, Lyons, & Tohen, 1997; Zanarini et al., 1998).

Course and prognosis. The course of BPD is highly variable, and seems to be less stable over time than expected for a personality disorder (Skodol et al., 2005) indicating a characteristic 'stable instability' (Schmideberg, 1947). The onset of the illness is usually in late adolescence or early adult life (Lieb et al., 2004), although the first contact with psychiatry services occurs much later. Nevertheless, especially for their early detection and possible prevention, recent evidence suggests that both maladaptive traits and contextual risks for BPD can be identified prior to adulthood (Crowell et al., 2005).

Table 1. BPD diagnostic criteria in the DSM-5 and in the DSM-IV-TR, and their equivalences. *PDC: Personality Disorder General Criteria*

DSM-5	DSM-IV
A. Moderate greater impairment in personality functioning, manifested by characteristic difficulties in two or more of the following areas:	**A. Pervasive pattern of instability of interpersonal relationships, self-image, affects and marked impulsivity as indicated by 5 (or more) of the following:**
1. ***Identity***: Markedly impoverished, poorly developed or unstable self-image, often associated with excessive self-criticism; chronic feelings of emptiness; dissociative states under stress 2. ***Self-direction***: Instability in goals, aspirations, values, or career plans 3. ***Empathy***: Compromised ability to recognize the feelings and needs of others associated with interpersonal hypersensitivity; perceptions of others selectively biased toward negative attributes or vulnerabilities 4. ***Intimacy***: Intense, unstable, and conflicted close relationships, marked by mistrust, neediness, and abandonment; close relationships often viewed in extremes of idealization and devaluation and alternating between over-involvement and withdrawal	3. ***Identity disturbance***: markedly and persistently unstable self-image or sense of self 7. Chronic feelings of ***emptiness*** 9. Transient, stress-related ***paranoid*** ideation or severe dissociative symptoms 2. A pattern of unstable and intense ***interpersonal relationship*** characterized by alternating between extremes of idealization and devaluation
B. Four or more of the following seven pathological personality traits (including at least one of the following: #5 Impulsivity, 6# Risk taking, or #7 hostility):	
1. ***Emotional lability***: unstable emotional experiences and frequent mood changes; emotions that are easily aroused, intense, and/or out of proportion to events and circumstances. 2. ***Anxiousness***: intense feelings of nervousness, tenseness, or panic, often reaction to interpersonal stresses; worry about the negative effects of past unpleasant experiences and future negative possibilities; feeling fearful, apprehensive, or threatened by uncertainty; fear of falling apart or losing control.	6. ***Affective instability*** due to a marked reactivity of mood (*e.g.*, irritability, intense episodic dysphoria)
3. ***Separation insecurity***: Fears of rejection by-and/or separation from-significant	1. Frantic efforts to avoid real or imagined ***abandonment***

others, associated with fears of excessive dependency and complete loss of autonomy.	
3. ***Depression***: frequent feelings of being down, miserable, and/or hopeless; difficulty recovering from such moods; pessimism about the future; pervasive shame; thoughts of suicide and suicidal behaviour.	5. Recurrent suicidal behaviour, gestures, or threats, or self-mutilating behaviour
5. ***Impulsivity***: acting on the spur of the moment in response to immediate stimuli; acting on a momentary basis without a plan or consideration of outcomes; difficulty establishing or following plans; a sense of urgency and self-harming behaviour under emotional distress. 6. ***Risk taking***: engagement in dangerous, risky, and potentially self-damaging activities, unnecessarily and without regard to consequences; lack of concern for one's limitations and denial of the reality of personal danger	4. ***Impulsivity*** in at least two areas that are potentially self-damaging (e.g. spending, sex, substance abuse, reckless driving, binge eating)
7. ***Hostility***: Persistent or frequent angry feelings; anger or irritability in response to minor slights and insults.	8. Inappropriate, intense anger or difficulty controlling ***anger*** (*e.g.* recurrent physical fights).
C. The impairment in personality functioning and the individual's personality trait expression are relatively inflexible and pervasive across a broad range of personal and social situations	*PDC* B: The enduring pattern is inflexible and pervasive across a broad range of personal and social situations
D. The impairments in personality function and the individual's personality trait expression are relatively stable across time with onsets that can be traced back at least to adolescence or early adulthood	*PDC* D: The pattern is stable and of long duration, and its onset can be traced back at least to adolescence or early adulthood
E. The impairment in personality function and the individual's personality trait expression are not better explained by another mental disorder	*PDC* E*:* The enduring pattern is not better for as a manifestation or consequence of another mental disorder.
F. The impairment in personality functioning and the individual's personality trait expression are not related to a substance (e.g. a drug of abuse, medication) **or a general medical condition** (e.g., severe head trauma)	*PDC* E: The enduring pattern is not due to the direct physiological effects of a substance or a general medical condition
G. The impairment in personality functioni and the individual's personality trait expression are not better understood as normal behaviour for the individual's developmental stage or socio-cultural environment	*PDC* A*: An* enduring pattern of inner experience and behaviour that deviates markedly from the expectations of the individual's culture

Despite BPD being a severe mental disorder, the prognosis is optimistic. A recent longitudinal study provided the evidence that, from the baseline until ten years later, 86% of BPD individuals have stable and sustained recovery from their symptoms [(Zanarini, Frankenburg, Reich, & Fitzmaurice, 2010a); see also: (Gutiérrez et al., 2012)]. Moreover, of those BPD patients who achieved recovery, only 5.9% experienced recurrences (Zanarini, Frankenburg, Hennen, & Silk, 2003). Importantly, this recovery is usually accompanied by improvement in work and social domains (Zanarini, Frankenburg, Hennen, Reich, & Silk, 2005). Thus even though BPD is considered a chronic condition, most patients tend to improve with time, and the majority of BPD patients show a normal functioning at the age of 40 years (Paris, 2002).

Treatment. Another important characteristic of BPD patients is that they usually require more mental-health resources than individuals with other psychiatric disorders (Bender et al., 2001), generating important social costs (van Asselt, Dirksen, Arntz, & Severens, 2007). Notice that, in the USA, 97% of BPD patients receive outpatient treatment from an average of six therapists (Skodol, Buckley, & Charles, 1983). Moreover, during the course of the disorder BPD people require a large amount of attention from their relatives, because they suffer important social and vocational impairment (Zanarini, Frankenburg, Reich, & Fitzmaurice, 2010b).

Although the treatment of BPD patients is very complex, there is more consistent evidence in favour of the psychological interventions most consistently than for the psychopharmacological ones (see for a recent review: (Stoffers et al., 2012). It is not surprising, then, that the UK National Institute for Health and Clinical Excellence in their 2009 guideline (NICE, 2009), recommends explicitly that '*drug treatment should not be used specifically for borderline personality disorder or for the individual*

symptoms or behaviour associated with the disorder (for example, repeated self-harm, marked emotional instability, risk-taking behaviour and transient psychotic symptoms)'. However, BPD patients are usually treated with polypharmacy (Lieb et al., 2004; Zanarini, Frankenburg, Hennen, & Silk, 2004).

On the other hand, psychological treatments are effective (Paris, 2010). Some treatment proposals are generic, such the Cognitive Therapy of Personality Disorders (Beck, Freeman, & Davis, 2006), but others are very specific to BPD. Certainly, the Dialectical Behaviour Therapy (Linehan, 1993) has been studied most intensely, followed by the Mentalization-Based Treatment (Bateman & Fonagy, 2004), the Transference Focused Therapy (Kernberg, 1967), the Schemas Focused Therapy (Young, 1994), and the System Training for Emotional Predictability and Problem Solving (Blum et al., 2008). Recently, shorter variants of these treatment models (*e.g.*, three-months skills training group of Dialectical Behavior Therapy) have shown clinical improvement and low dropout numbers, resulting cost effective interventions for BPD patients (Soler et al., 2009). In addition, there are several psychological interventions addressed to BPD relatives (Hoffman & Fruzzetti, 2007). Despite all these treatment options and the undoubtedly substantial role of psychotherapy plays in the treatment of BPD patients, replicative studies are needed (Stoffers et al., 2012).

1.2. Etiology

The causes of BPD remain unclear to date, having been suggested a complex interaction between neurobiological and environmental factors in their etiology having been suggested (Wingenfeld, Spitzer, Rullkötter, & Löwe, 2010).

First, BPD is greatly influenced by genetic factors (Distel et al., 2008, 2009) with concordance rates of 35% and 7% among monozygotic and dizygotic twin pairs

respectively, being their heritability estimated at .69 (Torgersen et al., 2000). Genes involved in the serotonin system are the most frequently linked to BPD (*e.g.*, Goodman & New, 2000), followed by those involved in the dopaminergic system (*e.g.*, Joyce et al., 2006). In addition, it has been suggested that the hipotalamus-pituitary-adrenal axis is altered in BPD patients, congruently with their heightened susceptibility to stress (*e.g.*, Carrasco et al., 2007; Wingenfeld et al., 2010). On the other hand, the majority of BPD patients report various types of adverse childhood experiences, such as sexual abuse, physical maltreatment or emotional neglect (Lobbestael, Arntz, & Bernstein, 2010; Zanarini, Gunderson, Marino, Schwartz, & Frankenburg, 1989). In fact, BPD is commonly comorbid with post-traumatic stress disorder (*e.g.*, Golier et al., 2003). Recently, Schwarze et al. (2013) also reported that adverse intrauterine conditions, such as exposure to tobacco, maternal traumatic stress or family conflicts among others, can be involved in the BPD etiology. Therefore, the early childhood environment plays an important role in the pathogenesis of BPD.

Additionally, in recent years, the idea of a dysfunctional reward and endogenous opioid systems in BPD has received growing interest (Bandelow, Schmahl, Falkai, & Wedekind, 2010). This possible alteration could explain some core symptoms of BPD. This hypothesis will be developed in posterior sections.

Integrating all these findings, it is currently assumed that deficits in affect regulation are the core of BPD (Skodol, Gunderson, et al., 2002; Skodol, Siever, et al., 2002). This idea is in accordance with the most influential theoretical model of BPD etiology, which is Linehan's Biosocial Theory (Crowell, Beauchaine, & Linehan, 2009; Linehan, 1987, 1993) [for other comprehensive approaches see for example: (Fonagy, Target, & Gergely, 2000; Judd & McGlashan, 2008)].

Linehan (1993) (see Figure 2) proposes that biological dysfunctions (*e.g.*, alterations in limbic brain regions) determine some clinical characteristics such as (a) heightened sensitivity to mild emotional stimuli, (b) inability to regulate intense emotional responses, and (c) a slow return to the prior emotional baseline (after emotional response). This supposes a biological vulnerability which interacts with certain early adverse environmental factors (*e.g.*, disabling environments). Continuous transactions between these biological vulnerabilities and environmental influences over time, ultimately, cause a characteristic global emotion dysregulation. Therefore, emotional dysregulation is considered the primary dysfunction in BPD (according to this model) and explains behavioural alterations (*e.g.*, self-harm), cognitive symptoms (*e.g.*, dissociation), interpersonal issues (*e.g.*, fear of abandonment) or distortions in the *self* (*e.g.*, emptiness). This prior Biosocial model has been updated recently (Crowell et al., 2009), incorporating several new biological findings (see Figure 2 for a schematic approach to this updated Biosocial theory model).

Another influential theoretical approach to BPD is the proposal by Kernberg (1967). His model considers the high prevalence of early traumatic experiences among these patients (*e.g.*, physical or sexual abuse), and their biological predisposition to negative affectivity (*e.g.*, alterations in the serotoninergic system). These two factors result in a: (a) syndrome of identity diffusion, (b) predominance of primitive defensive mechanisms centering on splitting, and in the (c) maintenance of reality testing. Thus, a lack of normal identity integration is evidenced by non-reflective, contradictory or chaotic descriptions of self and others and, also, by the lack of awareness of these contradictions. This results, for example, in a great difficult in emphasizing, in establishing sustained intimate relationships or in selecting appropriate partners. In addition, the predominance of primitive defensive mechanisms is manifested, for

example, by the characteristic distortion of the patient-therapist interaction and by the constant changes between idealization-devaluation perceptions. Finally, the maintenance of reality testing explain the capacity of BPD patients to easily accept easily their unreasonable, impulsive and chaotic behaviour.

The Mentalization Theory of BPD (Bateman & Fonagy, 2004) is also an influential model. Its emphasis is on the mentalization psychoanalytical concept which is, very briefly, 'the capacity to conceive of conscious and unconscious mental states in oneself and others' (Allen & Fonagy, 2006). This model suggests that (a) individuals are constitutionally vulnerable and/or exposed to psychological trauma, (b) both these factors can undermine the development of social/cognitive capacities necessary for mentalization in early relationships (especially where the contingency between their emotional experience and the caregiver's mirroring is non-congruent), (c) these all result in an hypersensitive attachment system within interpersonal contexts, and (d) this leads to the development of an weakened ability to represent affect and effort as weel as fully control attention capacity.

1.3. Personality

The classification of Personality Disorders in the DSM (fourth edition and previous) is the result of committee deliberation, therefore arbitrary, as it pays little attention to concepts resulting from the study of normal personality constructs (Livesley, Jang, & Vernon, 1998). This is a limitation for some authors (Widiger & Simonsen, 2005). There is evidence, besides, in favor of an appropriate representation of Personality Disorders using a dimensional model [see for some proposals: (Livesley et al., 1998; Widiger & Costa, 1994)]. Thus, in accordance with some authors, Personality Disorders might be understood as extreme variants of normal personality dimensions (Widiger & Mullins-Sweatt, 2009).

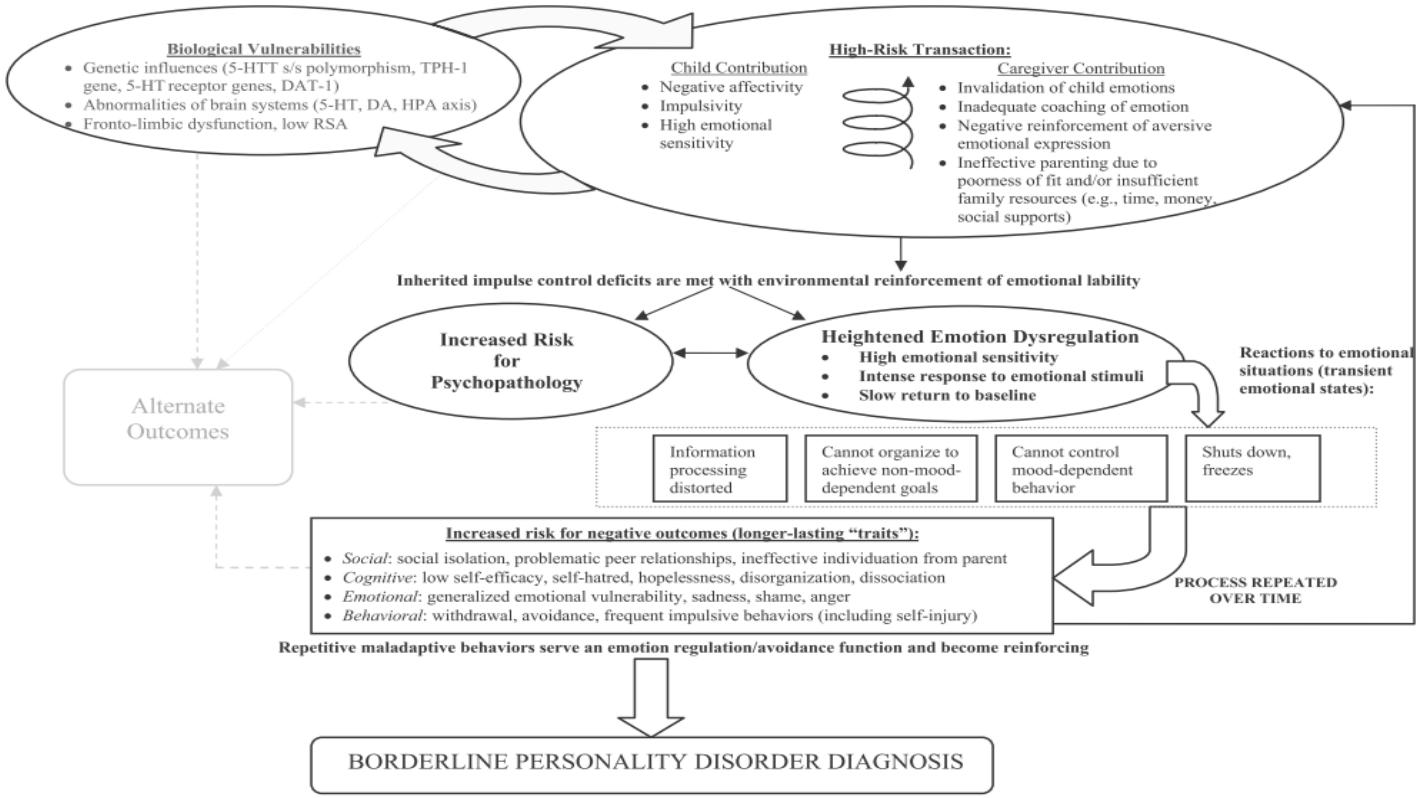


Figure 2. Biosocial model of BPD. Interaction between biological and environmental vulnerabilities lead to a heightened emotional dysregulation which facilitates alterations at cognitive level, these all being all these reinforced by the results of maladaptive behaviours and/or for the emotion regulation/avoidance (positive/negative reinforcement). *5-HT*: serotonin; *DA*: dopamine; *HPA*: hypothalamic–pituitary–adrenal; *RSA*: respiratory sinus arrhythmia. Figure from (Crowell et al., 2009)

From this perspective, using the Five-Factor Model (McCrae & Costa, 1987), BPD patients show high scores in neuroticism (*emotional instability*) and low scores in agreeableness and conscientiousness [see for a meta-analytic review: (Samuel & Widiger, 2008; Saulsman & Page, 2004)]. Therefore, congruently, they show a tendency to experience negative emotions, such as anger, anxiety or depression (high neuroticism) and also tend to show low self-discipline and a preference for spontaneous behaviour (low conscientiousness), as well as being suspicious, unfriendly and uncooperative (low agreeableness). The Five Factor Model has shown good discriminating ability regarding BPD and the Avoidant Personality Disorder (Wilberg, Urnes, Friis, Pedersen, & Karterud, 1999).

Using the Alternative Five-Factor Model (Zuckerman, 1991), Gomà-i-Freixanet and colleagues (Gomà-i-Freixanet, Soler, Valero, Pascual, & Sola, 2008) accurately described BPD in terms of having higher scores than controls on 'Neuroticism-Anxiety', 'Impulsivity-SensationSeeking' and 'Agression-Hostility', and lower scores on 'Sociability' and 'Activity'.

In an attempt to build a broad BPD dimensional profile, Pukrop (Pukrop, 2002) investigated dimensions derived from the Five Factor Model, Cloningers' psychobiological model (Cloninger, Svrakic, & Przybeck, 1993), and the bottom-up model proposed by Livesley (1998) by means of their corresponding self-reported measures [Five-Factor Test; Temperament and Character Inventory; Dimensional Assessment of Personality Pathology-Basic Questionnaire]. The main finding of this study was that BPD patients were characterized by high scores on Neuroticism, and Emotional Dysregulation and low scores in Self-Directedness (each of these dimensions correspond to each model respectively, and were inter-related). In addition, dimensions concerning social issues such as Agreeableness (Five Factor Model), Novelty Seeking

(Cloninger Model) or Dissocial Behaviour (Livesley Model) were specific markers for BPD patients regarding other Personality Disorders.

Despite the inherent interest and relevance of Gray's Reinforcement Sensitivity Theory [see for a review: (Corr, 2004)] this model has been studied little in BPD patients. This theory proposes the existence of two major motivational systems: the behavioural inhibition system (BIS) and the behavioural approach system (BAS). The first is sensitive to signs of punishment and unconditioned fear stimuli. The behavioural inhibition system activation has been related to the neuroticism personality trait and a tendency to experience negative affect. Contrary to this, the behavioural approach system organized behaviour in response to appetitive stimuli related to sings of unconditioned reward and non-punishment. Its activity has been related to impulsivity and with the tendency to experience positive affect (Bijttebier, Beck, Claes, & Vandereycken, 2009). Using the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (Torrubia, Avila, Caseras, & Molto, 2001), Mortensen and colleagues (Mortensen, Rasmussen, & Håberg, 2010) found that BPD patients obtained higher scores in Sensitivity to Punishment in relation to controls (suggesting a hyperactive BIS). Moreover, using BIS/BAS scales (Carver & White, 1994), BPD patients showed both BAS and BIS high scores, suggesting a hyper-activation of these two systems (Claes, Vertommen, Smits, & Bijttebier, 2009).

Here, is important to note that the original Reinforcement Sensitivity Theory has undergone a major reformulation over the past years (Gray & McNaughton, 2003). In the revised version, BAS is conceptualized in most aspects as in the original one; BIS is related to resolving conflicts, especially the approach-avoidance type but not to reactions to punishment as in the original model; finally, a third construct named Fight-Flight-Freeze System, that in many aspects is similar to the original BIS, is responsible

for reaction to all types of punishment. The original Reinforcement Sensitivity Theory adopted a separable subsystems hypothesis assuming that BIS and BAS were separable subsystems that operate independently of one another. In contrast to this assumption, (Corr, 2001) presented the joint subsystems hypothesis, which postulates that BIS and BAS could have interdependent or joint effects. Whereas the joint subsystems hypothesis is expected to be valid under certain human experimental conditions, it is believed that the separable subsystems hypothesis is more suitable in extreme personality groups or in cases where sensitivity to punishment and sensitivity to reward are both high (Bijttebier et al., 2009; Corr, 2001, 2004).

Following in a dimensional approach, interestingly, in the last years, specific measures to assess BPD traits have appeared in literature. Some examples are the Borderline Syndrome Index (Conte, Plutchik, Karasu, & Jerrett, 1980), the Borderline Personality Inventory (Leichsenring, 1999) or the Borderline Personality Questionnaire (Poreh et al., 2006). These measures comprise of specific symptoms of BPD clustered in dimensions such as 'Impulsivity', 'Affective Instability' or 'Abanadonment'. Similarly, several others were developed as part of a larger self-report measures such the Minnesota Multiphasic Personality Inventory-BPD scale (Morey, Waugh, & Blashfield, 1985) or the BPD scale from the Millon Clinical Multiaxial Inventory (Millon, 1992). Typically these specific measures have been used for assessing BPD traits in the community (Fonseca-Pedrero et al., 2011).

Finally, is important to take note of the fact that few studies have paid attention to possible bias in self-reported measures, such as personality inventories. In this vein, in clinical contexts, these measures are susceptible to being influenced or distorted by cognitive biases (i.e. socially desirability) or insight capacity, as has been previously shown when information obtained from the patient and close informants have been

directly compared (Klonsky & Oltmanns, 2006; Vazire, 2010). This discrepancy has been proposed as a tool for measuring the adequacy of self-knowledge (Vazire & Carlson, 2010) and has been related with personality dysfunction, co-morbidity, and treatment dropouts in clinical samples (Mosterman & Hendriks, 2011). Despite the inherent interest of this multiple-informant approach to investigate psychopathological conditions characterized by self-image disturbances, such as in BPD, this type of research has been scarce.

1.4. Neuropsychology

Many studies have investigated the neuropsychological functioning of BPD patients and, while most of them have reported impairment in a wide range of cognitive domains (Monarch, Saykin, & Flashman, 2004), the findings are not consistent (Kunert, Druecke, Sass, & Herpertz, 2003). Therefore, nowadays, the nature of the impairments encountered is under debate [for a review: (Dell'Osso, Berlin, Serati, & Altamura, 2010; Fertuck, Lenzenweger, Clarkin, Hoermann, & Stanley, 2006; Mak & Lam, 2013)].

Concretely, around 83% of the studies found impairment in one or more cognitive domain in BPD patients, involving deficits linked with the OFC and DLPFC (Legris & Reekum, 2006). Traditionally, well known tasks have been used for stabilising these alterations (*e.g.*, Continuous Performance Tests, Stroop test, Tower of London, Trail Making Test). There are suggested deficits in executive control, planning, working memory and long-term memory consolidation (Ruocco, 2005). The executive dysfunction in BPD has been related to behavioural discontrol, affective dysregulation, and social cognition problems presented in these patients (Legris, Links, van Reekum, Tannock, & Toplak, 2012; Sprock, Rader, Kendall, & Yoder, 2000; Travers & King, 2005). Interestingly, recently, it has been observed that these alterations can be

improved after a specific treatment (concretely the mindfulness dialectical behaviour therapy-module: (Soler et al., 2012) and, also, that these are related with treatment adherence [(preserved executive functions correlated positively with treatment adherence: (Fertuck et al., 2012)].

In addition, several studies have used motivational neuropsychological paradigms such as, for example, the Iowa Gambling Task (in which participants were encouraged to bet on four decks of cards being each trial reinforced or punished by an economical gain or loss). These types of studies have provided evidence in favour of poor/risky decision making and planning in BPD patients (Bazanis et al., 2002; Haaland & Landrø, 2007; Kirkpatrick et al., 2007; Lenzenweger, Clarkin, Fertuck, & Kernberg, 2004), which suggests alterations in the OFC (Burgess & Shallice, 1996). Importantly, the OFC has reciprocal connexions with the amygdala (Rushworth, Behrens, Rudebeck, & Walton, 2007), and is involved in affective dysregulation and impulsivity (Rolls, Hornak, Wade, & McGrath, 1994). Therefore, it has been proposed that BPD patients show neuropsychological deficits similar to patients with OFC lesions (Berlin, Rolls, Iversen, & Complete, 2005).

In contrast with all the above, many other studies have failed to find neuropsychological alterations in BPD (Dinn et al., 2004; Driessen et al., 2000). For instance, recently, Hagenhoff et al. (2013) found that, across different cognitive domains, working memory was the only altered executive function. In this study twenty eight BPD patients were compared with twenty eight non-patient controls on eight tasks (*e.g.,* n-back, go/no-go, continuous performance task). Consequently, authors proposed that the idea of a non-specific impairment in BPD patients that affects all domains of cognitive functions is erroneous. An expanded discussion on these interesting contradictory results will be done in later sections (see section 4).

1.5. Neuroimaging Data

Numerous neuroimaging studies have been conducted with BPD patients in recent years, providing interesting findings for the comprehension of the disorder although, sometimes, these have been contrary and inconclusive. Recently several reviews of structural and functional studies have been published (Mauchnik & Schmahl, 2010; McCloskey, Phan, & Coccaro, 2005; New, Perez-Rodriguez, & Ripoll, 2012; O'Neill & Frodl, 2012).

1.5.1. Structural changes

Amygdala and Hippocampus. The two most studied brain regions in BPD patients have been the hippocampus and the amygdala (see Table 2). On one hand, structural alterations in the hippocampus have been the most consistent alteration shown in these studies. The Hippocampus plays a role in memory consolidation, declarative memory, and is related to stress response (Bliss & Collingridge, 1993; McEwen, 1999; Squire, 1992). A prior study (Driessen et al., 2000) with twenty-one female BPD patients (eighteen inpatients and three outpatients; ranging from 21 to 40 years old; 57% presented a comorbid posttraumatic stress disorder) showed 16% smaller volumes of the hippocampus and 8% in the amygdala (in comparison to healthy controls). Since this first study (Driessen et al., 2000), many others have found significant hippocampal volume reductions bilaterally in BPD compared to healthy controls (Brambilla et al., 2004; Irle, Lange, & Sachsse, 2005; Schmahl, Vermetten, Elzinga, & Douglas Bremner, 2003; Tebartz van Elst et al., 2003; Zetzsche et al., 2006). Concretely, significant reductions in total hippocampal volume in BPD patients relative to controls ranged from approximately 14% (Schmahl et al., 2003) to 23% (Brambilla et al., 2004).

Table 2. Meta-analysis of structural changes in BPD brain. *Hipp*: Hippocampus; *Amy*: Amygdala; *PTSD:* Posttraumatic Stress Disorder

Study	Number or studies included (initial selection)	N (BPD/HC)	Age (BPD)	% Female (BPD)	% Medicated	% Comorbidity	Brain regions with volume reductions
Nunes et al (2009)	7 (104)	104/122	26.1-31[(1)]	97.11[(2)]	71.5[(2)]	42.9 PTSD [(2)]	Hipp / Amy
Hall et al (2010)	10 (189)	198/217	17.3-33.5[(1)]	---	---	---	Hipp / Amy
Rodrigues et al. (2011)[(3)]	7	124/147	26.1-33.5[(1)]	90 [(2)]	---	33.28 PTSD[(2)]	Hipp (PSTD>noPSTD)[(4)]
Ruocco et al. (2012)	11	205/222	30.4 ± 3.84	93.94 ± 13.81	70.68 ± 13.61	61.60 ± 28.79	Hipp (13%) / Amy (11%)
De-Almeida et al (2012)[(5)]	8	149/170	26.1-33.5[(1)]	86.8[(2)]	---	31 PTSD[(2)]	Amy (no PSTD>PSTD)[(6)]

[(1)] Age range calculated manually from the data available in the sample characteristics of each included study

[(2)] Calculated manually from the data available in the sample characteristics of each included study

[(3)] This meta-analysis was focused in studies that measured only hippocampal volumes in BPD

[(4)] Patients with PTSD showed a higher Hippocampus volume reduction than patients without PTSD

[(5)] This meta-analysis was focused on studies that measured only amygdalar volumes in BPD

[(6)] Patients without PTSD showed a higher Amygdala volume reduction than patients with PTSD

This reduction has been connected to elevated activity of the Hipotathalamic-Pituitary-Adrenal axis (HPA), because this axis is a major coordinator of the regulation of stress response and it is hyperactive after early trauma (Heim & Nemeroff, 2001), which fits well with BPD. Thus, upon stress exposure, corticotropin-releasing factor (CRF) is released from the hypothalamus and is transported to the anterior pituitary where it stimulates the release of adrenocorticotropin (ACTH), which in turn stimulates the synthesis and secretion of glucocorticoids from the adrenal cortex. Glucocorticoids act as negative feedback mechanisms. In the hippocampus there is a high density of Glucocorticoid receptors and, therefore, the hippocampus is not only an important mediator of stress response, but is also sensitive to the damaging effects of stress and glucocorticoids (Bremner, 1999). Nevertheless, although several studies have found alterations in the HPA axis of BPD patients (Carrasco et al., 2007) results are contradictory (Wingenfeld et al., 2010).

Concerning the Amygdala, however, results have been less consistent Thus, although several studies found a reduced volume compared to healthy controls (Schmahl et al., 2003; Tebartz van Elst et al., 2003), others have failed to show any difference (Brambilla et al., 2004; New et al., 2007), and some others showed an increased grey-matter volume (Minzenberg, Fan, New, Tang, & Siever, 2008). In addition, this possible volume alteration has been linked with the presence of a comorbid Major Depressive Disorder (Zetzsche et al., 2006). Of the studies which reported significant reductions in total amygdalar volume in BPD relative to controls, it ranges from approximately 8% (Driessen et al., 2000) to 24% (Tebartz van Elst et al., 2003).

Focusing on amygdala and hippocampus structural alterations in BPD patients, recently, several meta-analytic reviews have been published (de-Almeida et al., 2012;

Hall, Olabi, Lawrie, & McIntosh, 2010; Nunes et al., 2009; Rodrigues et al., 2011; Ruocco, Amirthavasagam, & Zakzanis, 2012). Table 2 shows the details of each meta-analysis involving the total number of studies included, the sample characteristics, the comorbidity of patients included (focusing on posttraumatic stress disorder) and the main results. Consistent with the above, all of these studies reported significant volume reductions for BPD patients bilaterally in these two brain regions. Despite this, additionally, Ruocco et al (Ruocco, Amirthavasagam, & Zakzanis, 2012) concluded that the reductions both in the amygdala and hippocampus may be unrelated to state-of-illness factors and to co-morbidity with other psychiatric disorders as, for example, PTSD [see also: (Weniger, Lange, Sachsse, & Irle, 2009)].

Anterior Cingulate Cortex (ACC). Beyond the Amygdala and hippocampus, the third most studied brain region has been the ACC, because it is involved in the regulation of emotion and cognitive control (Bush, Luu, & Posner, 2000). Since, for the first time, Tevartz van Elst et al. (2003) showed a volumetric reduction in the ACC grey matter of BPD patients compared to controls, other authors have replicated this finding (Hazlett et al., 2005; M. Minzenberg et al., 2008). In addition, interestingly, reduced ACC volume has been reported also in BPD adolescents (Goodman et al., 2011; Whittle et al., 2009), although not always (Brunner et al., 2010). In this interesting sub-group, Whittle et al. (2009) studied a sample of adolescents with first BPD presentation (mean age: 17.39 ± 1.15 years) who were less exposed to medication. A reduction of the ACC in the BPD patients was evidenced, which correlated negatively with non-suicidal self-injury behaviours, and positively only left ACC volume with impulsivity.

Other regions. Finally, other brain regions in which BPD patients showed volume alterations in comparison to healthy controls are the Putamen [Left; increased in BPD patients, (Brambilla et al., 2004)], the OFC [reduced in BPD, (Tebartz van Elst et al.,

2003); but this was not confirmed in a larger sample, (Rüsch et al., 2003)] and, also, the dorsolateral PFC in the context of impulsivity (Sala et al., 2011).

1.5.2. Functional changes

Research in this field is more contradictory, even when the same technologies are used (see for a recent review: (O'Neill & Frodl, 2012). This may be due, at least in part, to the high heterogeneity of BPD (Skodol, Gunderson, et al., 2002). In an attempt to minimize this potential confounding variable (heterogeneity), the exclusion criteria have been similar between studies (*e.g.*, major depressive disorder). Notice, however, that while this can increase the internal consistency of results it also could decrease their ecological validity.

Positron-emission tomography (PET). Most studies used Fludeoxyglucose (18F) (^{18}F-FDG), an analogue of glucose, for studying brain activity. Many of the studies analysed resting brain activity, which suppose that the PET was conducted while the participant did not have to perform any particular task (see Table 3). One example is the study of De la Fuente et al. (De La Fuente et al., 1997), which found significant reductions in resting state glucose metabolism in the premotor areas and the dorsolateral PFC, ACC, thalamus, caudate and lenticular nuclei of BPD patients compared to healthy controls. Only few PET studies have investigated brain glucose metabolism using specific tasks, in which participants were not at rest. For example, New et al. (New et al., 2009) showed that BPD patients with previous diagnoses of impulsive aggression, when performing an aggression inducing task, responded aggressively and showed heightened relative glucose metabolic rate in the OFC and the amygdala. Interestingly, metabolic rates were not elevated in dorsal PFC brain regions associated with cognitive control of aggression, as happened in the healthy control group.

Table 3. PET studies with BPD patients.

Study	Sample (BPD/HC)				Patient State	Medication status	Results
	N	Age (mean ± SD)	Gender (female)	Handedness (righ-handed)		Time free before the PET	BPD *vs* HC
De la Fuente et al. (1997)	10 / 15	34.2±7.2/30.7	8 /7	10 / 15	Resting	> 10 days	BPD<HC: premotor areas, PFC, ACC, Thalamic, Caudate and Lenticular nuclei
Soloff et al (2000)	5 / 8	28.4±10.1/ 28.6±11.1	5 / 3	4 /7	Resting	> 8 months	BPD<HC: R_ PFC (BA 10), L and Medial superior temporal gyrus (BA 22-23), L_Parietal lobe (BA 40) and L_Caudate body
Juengling et al (2003)	12 / 12	25±4/ 30±9	12 / 12	---	Resting	> 4 weeks	BPD>HC: FC and PFC BPD<HC: L_hippocampus, Cuneus
Soloff (2003)	13[(1)] / 9	25.2±7.1/27.4±6.4	13 / 9	13 / 9	Resting	Variable	BPD<HC: OFC (BA 9, 10, 11)
Oquendo (2005)	11[(2)] / 8 [(3)]	32±8.9/42.6±15.7	11 / 8	10 / 8	Resting	> 14 days; 6 weeks for fluoxetine; 1month for antipsychotic	$BPD_{(MDD)}$ >BPD : Parieto-Temporal regions $BPD_{(MDD)}$ <BPD: ACC
Lange (2005)	17 [(4)] / 9	32±4/33±6	17 / 9	---	Memory task	Five subjects were on antidepressant medication	BPD<HC: PCC
Soloff (2005)	22 / 24	$26.9_{(f)}$, $33.3_{(m)}$ / $29.6_{(f)}$, $25.1_{(m)}$	15 / 10	---	Resting	> 3 months	BPD<HC (male but not female): L_Temporal lobe

New et al (2007)	26 [5] / 24	30.7±8.6$_{(f)}$, 37.5±7.9$_{(m)}$ / 34±11.2$_{(f)}$, 31.7±7.9$_{(m)}$	9 / 9	19 / 19	Resting and placebo or resting and m-CPP	> 6 weeks	HC>BPD: coupling between OFC and amygdala (ventral)
New et al (2009)	38 / 36	30.5 ± 8.5/ 28.4±7.1	16 / 18	32 / 32	Laboratory induced aggression	> 2 months	BPD<HC: dorsal PFC BPD>HC: OFC, Amygdala
Salavert et al (2011)	8 / 8	35.5±9.27/32±7.86	6 / 5	8 / 8	Resting	> 1 month	BPD<HC: FC BPD>HC: motor cortex, medial and ACC, occipital lobe, temporal pole, L_superior parietal gyrus and R_superior frontal gyrus

Sample characteristics, patients' state in the moment of the PET (most frequently in a state of rest) and medication status are depicting. In the last column the main findings of each study are described considering hypometabolism (BPD<HC) and hypermetabolism (BPD>HC) results as required, taking into account the differences between BPD patients and HC participants (except for the study of Oquendo et al, 2005).

[1] BPD patients were very impulsive

[2] BPD patients have a co-morbid MDD

[3] Control group consisted of MDD patients without BPD

[4] BPD patients have history of childhood abuse and dissociative symptoms

[5] BPD patients have a co-morbid Intermittent Explosive Disorder

(f): female; (m): male; *BA*: Brodman Area; *MDD*: Major Depressive Disorder; *m-CPP*: meta-chloropiperazine; *BPD (MDD):* BPD with comorbid MDD

Although most studies seem to show less activity in the OFC and ACC in BPD patients relative to healthy control participants, other studies have suggested contradictory results (Juengling et al., 2003; Salavert et al., 2011). In addition, a dysfunctional connectivity between OFC and the amygdala in BPD patients has been proposed using PET (New et al., 2007). PET studies with BPD patients are summarized in Table 3.

Functional MRI (fMRI): Emotional Processing. The fMRI research has been focused on the study of emotional processing, because of its crucial role in affect regulation in BPD (Skodol, Gunderson, et al., 2002; Skodol, Siever, et al., 2002) (see Table 4). In this vein, given the importance of the fronto-limbic network in this process (Davidson & Irwin, 1999), it has been the focus of most studies [which involve the amygdala, the ACC, the OFC, the Hippocampus, and the dorsolateral PFC; see: (Davidson, Putnam, & Larson, 2000)]. Along with different methodologies and by using standardized (*e.g.* emotional slides from the International Affective Pictures System) or personalized (*e.g.* autobiographical slides) materials, the most common finding has been an exaggerated activity in the Amygdala of patients with BPD compared to controls during procedures that involve the processing of emotionaly aversive stimuli (Donegan et al., 2003; Herpertz et al., 2001; Minzenberg, Fan, New, Tang, & Siever, 2007). In addition, a weakening of prefrontal inhibitory control which could contribute to an enhanced hyperactivity in the amygdala has been suggested [see for a review: (Rosenthal et al., 2008)].

Interestingly, several studies have used emotionally valenced stimuli as 'distractors' in the performance of behavioural/cognitive tasks. For example, Silbersweig et al (Silbersweig et al., 2007) used an emotional-linguistic go/no-go task for studying the interaction between emotion and motor inhibition. Importantly, these

authors found that under the condition of behavioural inhibition (no-go) and negative emotion context (*e.g.* verbal stimuli containing themes salient for individuals with BPD), BPD patients showed a significant reduction in the ventro-medial PFC activity (including subgenual ACC) compared to controls. This region has been related to conflict detection and performance monitoring (error detection), it then suggest that BPD patients have behavioural descontrol under negative affect states. Congruently, by also using a go/no-go task, Jacob et al. (2013) demonstrated that anger induction (participants listened to an anger-inducing story) evoke stronger activation in the right amygdala and right nucleus subtalamics, and less activation in the subgenual ACC in BPD patients compared to healthy controls. Furthermore, in no-go trials after anger histories, only controls showed inferior FC activation, a brain area which is involved in behavioural inhibition. In this same line, another interesting study (Holtmann et al., 2013) used a modified Flanker task (Eriksen, 1995) for investigating how an irrelevant (not useful for the task itself) emotional stimuli (fearful faces) affect performance and fronto-limbic neural activity patterns during attention demanding cognitive process. In the within-subjects comparison, the BPD patients showed a hyperactivation of the right amygdala during emotional interference in the incongruent Flanker condition, accompanied with no deactivation of this brain region in the congruent condition. In addition, between-subject comparisons revealed that BPD patients showed increased activation in the ACC in those emotional *vs* neutral conditions than the control participants.

Despite the findings of all these studies, a recent meta-analysis (Ruocco, Amirthavasagam, Choi-Kain, & McMain, 2013) demonstrated that the results provided by fMRI studies are conflicting. In this meta-analysis, authors showed that healthy control subjects activated a well-characterized network of brain regions associated with

processing negative emotions that included the ACC and the Amygdala, while BPD patients activated a more diffused network of neural structures when negative *vs.* neutral task conditions where contrasted. Concretely, compared with healthy controls, BPD patients demonstrated heightened activity in the right insular cortex and the posterior Cingulate Cortex. Conversely, they showed less activation than control subjects in a network of regions that extended from the Amygdala to the Superior Temporal Cortex, the ACC and dorsolateral PFC. These results, despite being congruent with structural neuroimaging findings of a reduced volume of the Amygdala (see structural MRI section), are inconsistent with previous fMRI individual studies (Donegan et al., 2003; Koenigsberg et al., 2009; Minzenberg, Fan, New, Tang, & Siever, 2007) and narrative reviews (McCloskey et al., 2005), above all when concerning the Amygdala.

In Figure 3 the main results of this meta-analysis (Ruocco et al., 2013) for healthy controls, BPDs and for BPD *vs* healthy controls contrast can be observed.

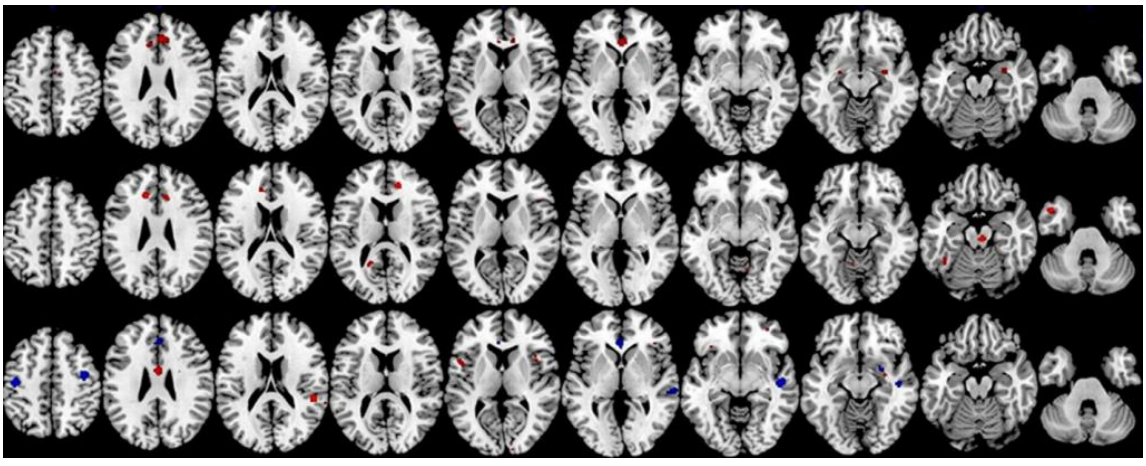


Figure 3. Activation-likelihood-estimation contrast maps of negative emotion-neutral test for control subjects (top row), BPD (middle row) and BPD – control subjects (bottom row). Maps are based on a false discovery rate-corrected threshold of $p < .05$ and a minimum cluster threshold of 100 mm^3. Areas showing higher activation are in red; lower activation in blue. From Ruocco et al. (2013)

For Ruocco et al. (2013), the observed abnormal relationship between limbic and anterior brain regions might explain the negative processing alterations of BPD patients.

Therefore, greater activation in the Insula (relative to controls) suggests alterations in the subjective experience of negative emotions and in their "top-down" control (Diekhof, Geier, Falkai, & Gruber, 2011; Phillips et al., 2004). In addition, increased activity in the left inferior frontal gyrus might also suggest a disruption of frontal systems involved in cognitive control, because this region is commonly associated with response inhibition (Swick, Ashley, & Turken, 2008). Thus, heightened activity in this cortical region during negative emotion processing could denote a deficiency in inhibitory mechanisms involved in the modulation of emotion. Congruently, the reduction in the activity of the subgenual ACC (BA 25) observed in BPDs, suggest a diminished capacity for regulating emotions, due to this brain region being involved in the cognitive control of emotions (di Pellegrino, Ciaramelli, & Làdavas, 2007; Drevets, Savitz, & Trimble, 2008). Finally, the bilateral reduction in the activity of dorsolateral PFC suggest alterations in the cognitive control capacities required for the modulation of subjectively experienced negative emotions (Banks, Eddy, Angstadt, Nathan, & Phan, 2007).

Because affective instability is not an exclusive characteristic of BPD, but also, for example, of bipolar disorder, or MDD for example (Koenigsberg, 2010), recently, several other studies have focused on the investigation of different BPD core aspects (social cognition, pain and reward).

Table 4. Summary of the fMRI studies which used emotionally negative paradigms

Study	Sample (BPD/HC)				Paradigm	Medication status	Main results
	N	Age (mean)	Gender (female)	Handedness (righ-handed)			(between, within subject contrast)
Beblo et al (2006)	20/21	31.3±8/ 32.6±7.8	20/21	---	Autobiographical memory were stimulated by cue words	12 patients were in treatment	BPD>HC, unresolved *vs* resolved life events: Insula , Amygdala, ACC and Temporo-medial areas
Guitart-Masip et al (2009)	10/10	31.3±9.47/ 31.2±9.05	5/5	10/10	Emotional discrimination task (negative *vs* neutral faces)	> 2 months	BPD>HC, negative *vs* neutral faces: Posterior Temporal cortex
Herpertz et al (2001)	6/6	26.2±8.1/ 27.2±4.5	6/6	6/6	Perception of photographs (highly arousing unpleasant *vs* neutral)	Free in the moment of the experiment	BPD>HC, negative *vs* neutral photographs: Amygdala, Fusiform gyrus,
Koeningsberg et al (2009)	19/17	34.9±11.1/ 31.2±10.6	7/8	14/15	Perception of photographs portraying aversive (negative) vs neutral interpersonal situations	>2 weeks (6 in the case of fluoxetine)	BPD>HC, negative *vs* neutral: L_Amygdala, Fusiform gyrus, superior temporal gyrus HC>BPD, negative *vs* neutral: DLPFC
Kraus et al (2010)	11/10[(1)]	25.6±3.63/ 25.6±5.23	11/10	---	Script-driven imagery (self-injury) to induce a negative *vs*. neutral emotional state	>2weeks	BPD>HC, negative *vs* neutral: DLPFC HC>BPD, negative *vs* neutral: OFC, PCC
Minzenberg et al (2007)	12/12	30.3±8/ 30.7±10	7/6	---	Photographs of faces with angry, fearful and neutral expressions	Free at the moment of the experiment	BPD>HC, fear *vs* neutral: R_Amygdala HC>BPD, fear *vs* neutral: ACC BPD>HC, anger *vs* neutral: ACC

							HC>BPD, anger *vs* neutral: Amygdala
Schnell et al (2007)	6/6	23.7±4.8/ 23.4±5	6/6	---	Perception of negatively valenced drawings *vs*. neutral photographs	>4 weeks	BPD>HC, negative vs neutral: DLPFC and Dorsomedial FC
Schulze et al (2011)	16/16	27.6±7.85/ 24.5±2.85	16/16	---	Perception of negative vs. neutral photographs	>2weeks	HC>BPD, negative *vs* neutral: R_Insula, temporal gyrus, superior frontal gyrus,
Silbersweig et al (2007)	16/14	31.25/23.8	15/10	15/12	Emotional lexical go/no-go task	11 patients were in treatment	BPD<HC, negative *vs* neutral for no-go trials: sgACC, VmPFC
							BPD>HC, negative *vs* neutral for no-go trials: Amygdala, VS
Smoski et al (2011)	12/12[(2)]	32.8±13.9	0/0	10/10	Emotional "oddball" task containing neutral and negative photographs	---	BPD<HC, negative *vs* neutral: Amygdala, hippocampus, ACC, sgACC
							BPD>HC, negative *vs* neutral: L_Inferior_frontal gyrus
Wingenfeld et al (2009)	20/20	29.7±13.2/ 29.4±12.4	14/14	---	Emotional Stroop containing words that were neutral, negative, or related to a past negative life event	All in treatment	HC>BPD, negative *vs* neutral: ACC and Frontal and Temporal brain areas
							HC, negative *vs* neutral: ACC and FC areas
Jacob et al (2013)	17/18	28.9±7.7/ 28±6.9	17/18	17/18	Performance on a Go/no-Go task after emotional induction (history of anger, joy or neutral)	4 were on med	HC>BPD, anger vs neutral for no-go trials: Inferior FC
							HC<BPD, anger vs neutral for no-go trials: Nucleus subtalamics
Krause-Utz et al (2012)	22/22	28.18±7.02 /27.4±8.5	22/22	22/22	Accuracy in the Working Memory task while neutral or negatively arousing pictures were presented as	>14 days (28 days for Fluoxetine)	BPD>HC, negative vs neutral: Amygdala, hippocampus, Insula

					distractors		
Kamphausen et al (2013)	13/15	29.31±5.45 /32±8.83	13/15	---	Fear learning by exposition to threatening and safe stimuli	2 patients in treatment	BPD>HC, threat *vs* save: Amygdala
Holtman et al (2013)	16/24	25.56±4.7/ 26.83±5.35	16/24	16/24	Performance in a modified Flanker Task with emotional stimuli (fear vs neutral faces)	>2 weeks (6 weeks for fluoxetine)	BPD, fear *vs* neutral in incongruent trials: R_Amygdala BPD>HC, fear minus neutral: ACC
Lang et al (2012)	14/15[3]	27.21±7.6/ 24.73±5.6	14/15	27.43/28.21[4]	Confronting emotional states (elicited by negative scripts) by instruction of increased (up), decreased (down) or not intervene (maintain) it	>2 weeks	BPD<HC, up *vs* maintain: ACC, PFC, PCC BPD<HC, down *vs* maintain: ACC

Note. fMRI studies which used emotionally negative paradigms. (from January 2000 to August 2013) which includes BPD patients diagnosed according to DSM (third edition or later) using a valid interview (*e.g.* Diagnostic Interview for Borderlines, Structured Clinical Interview for DSM-IV). In accordance with a previous meta-analysis (Ruocco et al., 2013) those studies which exceeded 50% of the co-morbid PTSD was excluded. In the 'main results' column the between-subjects (BPD>HC or BPD<HC) and within-subject contrasts are show. Following each one, the brain regions with increased activity are listed. *HC*: Healthy Controls; *PFC*: Prefrontal Cortex: *FC*: Frontal Cortex; *ACC*: Anterior Cingulate Cortex; *PCC*: Posterior Cingulate Cortex; : *sgACC*: Subgenual Anterior Cingulate Cortex; *VmPFC*: Ventro Medial Prefrontal Cortex; *DLPFC*: Dorsolateral Prefrontal Cortex; *VS*: Ventral Striatum; *L_*:Left; *R_*:Right

[1] All patients have SIB (self-harm by cutting was the most frequent)

[2] BPD patients were also opioid dependents

[3] This study includes 43 women: 14 trauma-exposed BPD patients (without PTSD), 14 trauma-exposed healthy subjects (without non-PTSD), and 15 non-traumatized healthy subjects. Table shows the comparison between BPD and non-traumatized HC group

[4] Values of the Edinburgh Handedness Scale

Functional MRI (fMRI): social cognition. Despite interpersonal problems being core aspects of BPD (Gunderson, 2007), they have received little fMRI attention [see for a review: (New et al., 2012)]. Nevertheless, findings in this field support aberrant social cognition in these patients [see for a review: (Roepke, Vater, Preißler, Heekeren, & Dziobek, 2012)], which is potentially is very important due to the fact that most of the prominent symptoms of BPD appear in the interpersonal context (*e.g.*, self-injury, emotional reactivity). These alterations are focused on the processing of simple social cues, such as less money. On the behavioural level, BPD patients showed a profound incapacity to maintain cooperation. In addition, BPD patients failed to regain trust and cooperation after their rupture. Importantly, controls showed a negative linear correlation between activation of the anterior Insula and both magnitude of monetary offer received from their partner (input) against the amount of money repaid to their partner (output). In contrast, response of the anterior Insula of the BPD patients was only related to output but not to input. Because the anterior Insula is a region involved in norm violations across affective, interoceptive, economic, and social dimensions, this data suggests alterations in the perception of social gestures in BPD.

Recently, Roepke et al. (2013) have developed an integrated framework for social cognition in BPD, which is presented in Figure 4. As can seen, as receivers of social signals, BPD patients present biases in cognitive empathy [deficits in the ability to infer the emotions, thoughts, and intentions of others; *e.g.*: (Dziobek et al., 2011; Preißler, Dziobek, Ritter, Heekeren, & Roepke, 2010)] and emotional empathy impairment [suggesting difficulties in the appropriate emotional reaction to another person; *e.g.:* (Dziobek et al., 2011)]. High arousal and comorbid posttraumatic stress disorder might interfere with BPD patients' ability for cognitive empathy (Preißler, Dziobek, Ritter, Heekeren, & Roepke, 2010). On the other hand, as senders of social

signals, BPD patients show deviant facial emotional reactions to social stimuli (Herpertz et al., 2001; Staebler et al., 2011). Alterations in the reception and sending of social information would facilitate a vicious cycle which, in turn, might lead to interpersonal conflicts that provoke aggressive outbursts, repetitive suicidal behavior or self-injury among other typical BPD behaviors. Repetitive interpersonal conflicts with significant others lead, therefore, to consequent difficulties in establishing stable long-term relationships.

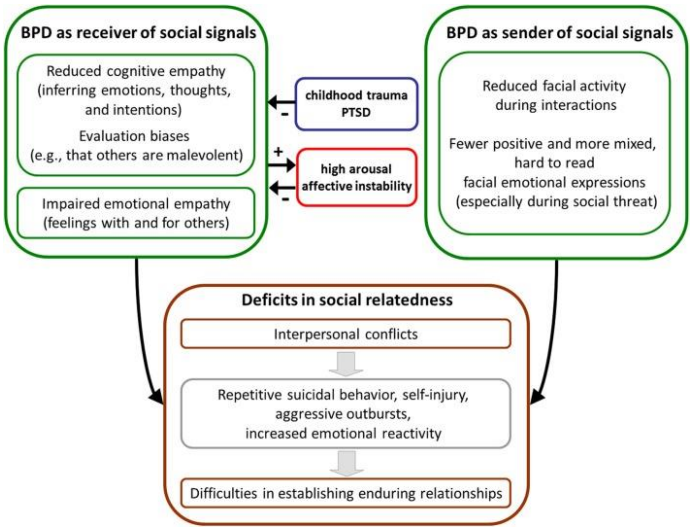


Figure 4. The boxes show the possible links between social expression, social information processing and their consequences in the interpersonal field. Reproduced from Roepke et al. (2013)

Functional MRI (fMRI): pain. Reduced pain sensitivity has been showed in the BPD, becoming an interesting field of study which is also associated with dissociative symptoms (Bohus et al., 2000). In particular, most BPD patients report that they do not feel pain during self-mutilation such as cutting (Russ et al., 1992), which is an important insight into understanding the role of self-injury in affect regulation (Niedtfeld et al., 2010).

Schmal et al. (2006) investigated twelve BPD patients with self-injurious behaviors *vs.* twelve age-matched controls subjects while a painful stimulus was applied to their hands. In response to this painful stimulus, BPD patients (compared with healthy controls) showed increased activations in the DLPFC and decreased activations

of the posterior parietal cortex. Additionally, pain evoked deactivation of the pregenual ACC and the amygdala in BPD patients. The interaction between increased pain-induced response in the dorsolateral PFC and deactivation in the ACC and the amygdala was suggested to be associated with an antinocioceptive mechanism in patients with BPD. A posterior study supports only partially these results because, using painful stimuli, the deactivation in the right Amygdala was associated with the presence of posttraumatic stress disorder in BPD patients (Kraus et al., 2009).

Functional MRI (fMRI): reward. Studies of the reward brain system are presented in posterior sections.

1.5.3. Connectivity changes

White matter connectivity: diffusion tensor imaging (DTI). The few DTI studies into BPD provide inconclusive results. A reduced Fractional Anisotropy (FA) in the OFC (Carrasco et al., 2012) and diminished inter-hemispheric connectivity in BPD along with comorbid attention deficit hyperactivity disorder (Rüsch et al., 2010) have been proposed, which suggest damage in the connectivity tracts in these brain areas.

Recently it has been proposed that FA responds to developmental factors. Thus, it might increase in adolescence and decrease in the adulthood, showing a U-shape curve (FA x age) (New et al., 2013).

In addition, BPD patients with self-injurious behaviors showed decreased white matter micro-estructural integrity in inferior frontal brain regions that may include components of orbito-frontal circuitry (Grant et al., 2007). Authors linked this finding with the inability to balance the desire for immediate gratification with the recognition of the long-term consequences.

Functional connectivity: Default Mode Network (DMN). The DMN comprises of the medial PFC, the posterior Cingulate/retrosplenial cortex (RSC) including the precuneus, the inferior parietal lobe, the lateral temporal cortex, and hippocampal formation (Buckner, Andrews-Hanna, & Schacter, 2008). Activity within the DMN has been observed when individuals are at rest or engaged in stimulus-unrelated thought.

BPD Patients showed differences in functional connectivity in the DMN. The abnormal DMN connectivity was restricted to particular brain regions: cuneus, Insula and Fronto-Parietal cortex. These regions are involved in several important functions as well as social cognition and emotional regulation, among others (Wolf et al., 2011).

Interestingly, alterations in the DMN have been also reported in response to painful stimulation (Kluetsch, Schmahl, Niedtfeld, & et al, 2012). In particular, Nietfeld et al. (2012) found that the pain improves the inhibition of limbic activity in PFC areas showing that, under pain stimulation, there was a negative coupling between neural areas associated with the processing of emotions (*e.g.*, left amygdala) and those which regulate the negative affect (*e.g.*, pregenual ACC). These results suggest a different cognitive and affective appraisal of pain in these patients than otherwise healthy controls.

1.5.4. Event Related Potentials (ERP)

ERP studies have focused on investigating the effects of the feedback as well as error processing in BPD patients, providing interesting findings. These studies are summarized in posterior sections.

2. Non-suicidal self-injury behaviour

One of the most prominent symptoms of BPD is the presence of non-suicidal self-injury (NSSI) behaviour [presented in 69-90% of cases: (Zanarini, 2007; Black, 2004)]. NSSI behaviour (also referred as self-mutilation, self-harm or self-injurious) refers to the deliberate, self-inflicted destruction of body tissue without suicidal intent, and for purposes not socially sanctioned (*e.g.* tattoos or piercings) (Klonsky, 2007; Nock & Prinstein, 2004). Importantly, these behaviors are different to suicide attempts (accordingly to the above definition) and to risk-taking behaviour (*e.g,*. skydiving, smoking tobacco). NSSI behaviour is not restricted to BPD, suffering it only about 50% of those who engage in NSSI suffer from it (Herpertz, 1995; Nock, Joiner, Gordon, Lloyd-Richardson, & Prinstein, 2006). Therefore, NSSI are present in other psychiatric [*e.g.*, major depression or eating disorders: (Langbehn & Pfohl, 1993; Paul, Schroeter, Dahme, & Nutzinger, 2002)], as well as genetic [*e.g.*, Lesch-Nyhan syndrome, Prader-Willy syndrome: (Anderson & Ernst, 1994)], neurological [*e.g.,* Tourette's syndrome: (Robertson, Trimble, & Lees, 1989)] and developmental conditions [*e.g.*, mental retardation, autism: Oliver, 1995)]. Self-harming methods in NSSI include, for example, cutting/carving, burning, biting, scraping/scratching skin, hitting, interfering with wound healing and skin picking (Klonsky, 2011).

There is evidence of an increasing frequency of NSSI behaviour in the general population, the onset being between the ages of 12 and 15 (Yates, 2004). Rates of NSSI are estimated at 4-6% in the adult general population and 20% in adult patient population (Briere & Gil, 1998; Klonsky, Oltmanns, & Turkheimer, 2003). Surprisingly, about 13-45% of adolescents have engaged in some NSSI at some point in their lives (Lloyd-Richardson, Perrine, Dierker, & Kelley, 2007; Plener, Libal, Keller,

Fegert, & Muehlenkamp, 2009). Importantly, NSSI plays an important role as prospective predictor of suicide attempts in adolescents (Asarnow et al., 2011; Wilkinson, Kelvin, Roberts, Dubicka, & Goodyer, 2011) and adults (Cooper et al., 2005; Murphy et al., 2012). Notice that suicide is a public health concern in western countries (Desjarlais, Eisenberg, Good, & Kleinman, 1995), because it is estimated that one million people worldwide commit suicide each year (Krug & Organization, 2002).

Nowadays, it is poorly understood why people (and animals) harm themselves, especially when it goes contrary to the evolutionary assumption that all animals fight innately for self-preservation (Dellinge-Ness & Handler, 2006). Furthermore, NSSI behaviour goes against the common principle to approach/maximize pleasure and avoid/minimize pain which normally governs our conduct (Gray & McNaughton, 2003; Kahneman & Tversky, 1979).

When attempting to better understand this 'paradoxal' behaviour, it is important to take into account that NSSI is not exclusive to humans. Thus, for example, non-human primates show stereotypical and abnormal behaviour which, in some cases, is extreme NSSI behaviour such as ripping finger and toenails, rubbing genitals on sharp objects, and repeatedly mutilating rectums (Lutz, Well, & Novak, 2003). Lifetime prevalence rates for NSSI in individually housed macaques have been estimated between 5 and 28 percent (Fritz, Nash, Alford, & Bowen, 1992). Interestingly, the NSSI phenomenon shows some similarities between non-human primates (basically captive animlas in zoos and research labs) and humans. Thus, for example, adolescence is a critical period in both cases (increasing with severity in non-human primates), isolation increases their prevalence (*e.g.*, incarcerated humans and captive monkeys) and there is an association with negative life experiences (*e.g.*, emotional neglect in humans, repeated experimentation and/or certain social experiences in the first two years of life in non-

human primates) [see for a review: Dellinge-Ness & Handler, 2006]. Because of these similarities, it has been proposed that biological NSSI basis in non-human primates could be useful in the understanding of this phenomenon in humans. Thus, in monkeys, adverse early experiences (*e.g.,* early social separation) followed by later repeated stressful events (*e.g.,* veterinary procedures) can result in lasting alterations in neuropeptide and neuroendocrine systems associated with the regulation of stress and anxiety. This dysregulation contributes to periodic episodes of heightened anxiety which lead to NSSI behaviours which, in turn, would serve to counteract these feelings of anxiety by eliciting euphoria associated with the release of endogenous opioids (Tiefenbacher, Novak, Lutz, & Meyer, 2005) (see the next section for an analogous description in humans).

2.1. Functions

The idea that the NSSI are a maladaptive attempt to self-regulate negative affect has received the most theoretical and empirical attention (Chapman, Gratz, & Brown, 2006; Linehan, 1993; Nock, 2009). In accordance, for example, self-injurers have shown a higher decrease in negative arousal (anger) following a strong physical shock (Weinberg & Klonsky, 2012), which suggests a causal link between self-injury and the reduction of negative arousal. Moreover, people who engage in NSSI have higher levels of neuroticism (MacLaren & Best, 2010), and are more reactive to emotional stimuli and less able to access affective strategies to regulate their emotional experience (Klonsky, 2007). Furthermore they show a lack of skills to cope with their negative affect (Fikke, Melinder, & Landrø, 2011; Nock & Mendes, 2008).

Therefore, although historically self-injury was understood as a tension-release or as a method for getting attention from others [see for example: (Favazza, 1989)], more

recently, empirical studies have focused on functions of NSSI, which involves taking into consideration their antecedent and consequent events that may have influenced these behaviours (Chapman et al., 2006; Klonsky, 2007; Nock & Prinstein, 2004). One of the most recent proposals in this line, suggested by Nock (2004; 2009; 2010), emphasizes a set of risk factors that increase the probability of engaging in NSSI behaviours, based on the findings from research done in this field. In accordance with this model (see Figure 5), these vulnerability factors facilitate dysfunctions in the stress regulation response, and NSSI behaviours appear as a coping strategy for a particular stressful event (*e.g.*, feeling abandoned). Consequently, NSSI behaviours act as a distress regulation strategy which is maintained over time by reinforcement feedback (*e.g.*, after cutting myself the feel of abandoned disappeared, because others are caring for me; see also Figure 6). In addition, other specific vulnerability factors contribute to NSSI (potentiating stress regulation dysfunctions). Thus, a person can engage NSSI behaviours because he/she: (a) is imitating friends or siblings, or being influenced by the media (social learning hypothesis), (b) is punishing himself for a perceived wrong-doing (self-punishment hypothesis), (c) has a positive attitude about these behaviours when regarding other available options (implicit attitude/identification hypothesis), (d) is signalling distress to others, searching for help from others (social signalling hypothesis), (e) is stimulating their endogenous opioid system (pain analgesia/opiate hypothesis), or simply (f) is choosing an effective and faster self-regulation strategy than others (pragmatic hypothesis). Figure 5 shows this integrated model graphically.

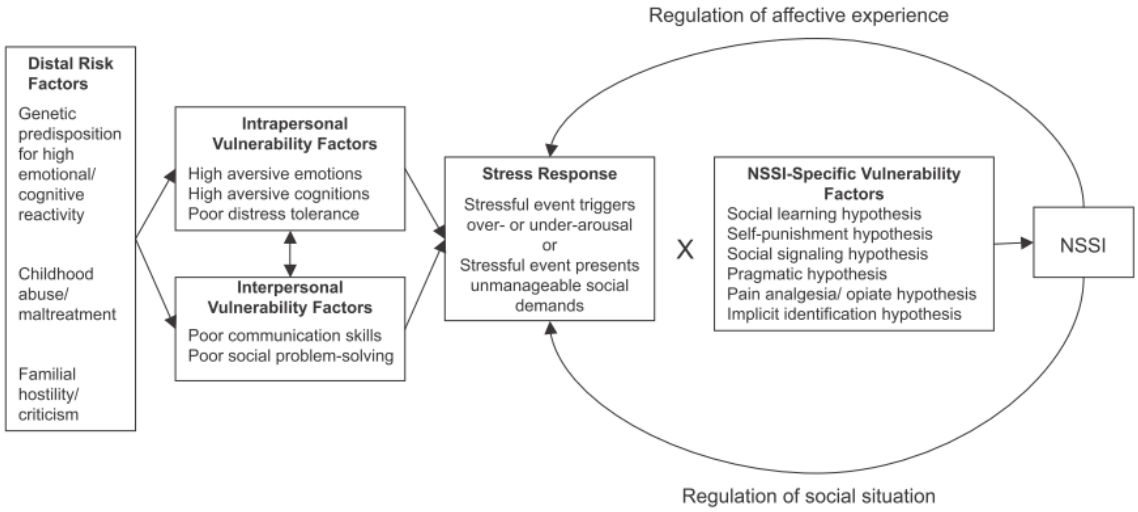


Figure 5. Integrated model of the development and maintenance of NSSI developed by Nock (2009, 2010). From left to right, the schema shows the general risk factors (*e.g.* childhood maltreatment) which favour vulnerabilities at intrapersonal and/or interpersonal level (*e.g.* poor distress tolerance or poor communication skills). Both these types of vulnerability factors facilitate dysfunctions in the stress regulation response, and NSSI behaviours appear as a coping strategy for a particular stressful event (*e.g.* feeling abandoned).

With regard to how NSSI behaviours are maintained over time, Nock (2010) proposed a functional approach by considering two dimensions, (a) reinforcements and (b) contingencies. Under this approach, basically, self-injurers repeatedly harm themselves searching for a desired result which can be the affective/cognitive self-regulation and/or the desire to have an impact in their close social environment (see Figure 6). An illustrative example, according to this model, is the case of a hypothetical person who suffers alcohol dependence in long remission: '*After a relapse, John feels guilt, sadness and anxiousness. When he explains the relapse to his wife, his anxiety increases and he experiences deep distress. In this moment, in private, he cuts himself causing a serious wound in his arm. This self-injury behaviour calms his distress and shows to his wife that, for him, the relapse has been as frustrating as for her. Immediately, also, their attention changes from the relapse to the wound and they stop talking about it'*. This example shows that a NSSI behaviour is associated with different

reinforcements. Thus, first, there is a reduction in distress arousal (negative reinforcement associated with an intrapersonal contingency: feeling better), second, the NSSI behavior acts to change the interpersonal scenario (interpersonal contingency) demonstrating, on one hand, the suffering and guilt (positive reinforcement: receiving attention and support) and, on the other, focusing the attention on a new problem (i.e. the physical injury; negative reinforcement: avoiding the conflict). Importantly, in the long-term, NSSI behaviours are reinforced repeatedly, leading to other more adaptive behaviours such as assertive communication, frustration tolerance abilities or distress tolerance being discarted.

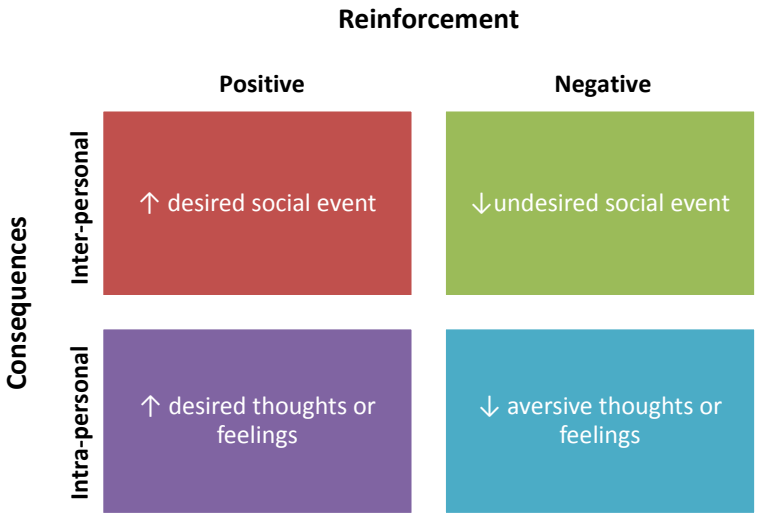


Table 6. Functional approach to NSSI from four possible reinforcement processes to NSSI considering two dimensions [based on: (Nock, 2010)]. On one hand, on the top, the type of reinforcement is (positive/negative) and, on the other, the possible consequences at intrapersonal/interpersonal level. This model results in a 2x2 matrix.

2.2. NSSI behaviors in the BPD

Considering the functional approach to the NSSI (see Figure 6), one can suppose that the BPD patients commonly present different combinations of reinforcements and

contingencies (section 1 describes the main BPD symptoms). Self-reported reasons for NSSI in BPD patients are affect-regulation, anti-dissociation (*e.g.* 'feel alive'), influence at interpersonal level, self-punishment or sensation-seeking among others (Brown, Comtois, & Linehan, 2002; Klonsky, 2007).

Beyond their functionality, the specific mechanisms by which NSSI leads to a change in affect are still unclear. In an attempt to resolve this association, most studies have focused on BPD as prototype of the use of NSSI behaviours. Despite the current advances in this field being only preliminary and scarce, there are some promising findings. Nowadays, cognitive control mechanisms and the opioid endogenous/reward system are received the most research attention.

Cognitive Control. In accordance with the above, BPD patients may be more likely to engage in rash actions, like NSSI, while experiencing intense negative affect. Thereby, when BPD patients with NSSI history listened to a standardized script describing a stressful situation and then heard a following a self-injury act, they presented a stronger deactivation of the OFC, relative to healthy controls (Kraus et al. 2009) (see also Table 4). Concretely, the paradigm used by these authors included: (a) neutral section (describes a woman on a shopping tour), (b) trigger situation (describes the woman watching a dispute between a mother and her child), (c) emotional and cognitive section (includes woman's ruminations concerning similar negative experiences with her mother), (d) NSSI section (describes preparation and the cutting itself), and (e) relaxation section (decrease in aversive inner tension). The OFC deactivation observed may be related to a failure to inhibit or modulate their emotional or cognitive reactivity, which in turn, may increase the urge for NSSI as an alternative way to reduce their tension. In agreement with this idea, an association between the presence of NSSI and the ACC volumes (which is involved in response inhibition and

action monitoring; see section 4) at structural level was found in BPD patients (Tebartz van Elst et al., 2003).

Besides this, interestingly, a reduction in the ACC in the BPD patients was evidenced in structural neuroimaging studies. This volume correlated negatively with NSSI behaviours, and positively (only left ACC volume) with impulsivity (Whittle et al., 2009) (this study was already discussed in a previous section). This finding is very important, because it demonstrates that the ACC is involved both in NSSI and impulsivity.

Endogenous opioid system (EOS) and dopaminergic reward system self-stimulation. It is proposed that many of the symptoms (*e.g.,* drug abuse, risky sexual contacts or disrupted interpersonal attachment) and NSSI of BPD may be explained by sufferers' uncontrollable and unconscious attempts to stimulate their EOS and the dopaminergic reward system, in the shortest possible time (see Figure 7) (Bandelow et al., 2010; Stanley & Siever, 2009). Importantly, EOS and the reward system are closely related due to opioids being implicated in the modulation of reward. Thus, opioids (β-endorphin, enkephalins, dynorphins and endomorphins) modulate mesolimbic dopamine pathways through the ventral tegmental area and nucleus accumbens by activating opioid receptors (μ-, δ-, and κ-) on secondary interneurons, causing hyperpolarization and inhibition of GABA release on dopaminergic output neurons with consequent increased dopamine release (Roth-Deri, Green-Sadan, & Yadid, 2008). Therefore, increases in μ- and δ- receptors are associated with hedonic properties of reward (Barbano & Cador, 2007), and their blocking (pharmacologically) reduces pleasure in rewards and increases the unpleasantness of losses (Petrovic et al., 2008).

Research has been focused on pain processing, due to a decreased sensitivity to painful stimuli being shown in self-injurers (Nock & Prinstein, 2004) and, in particular, in BPD patients (Bohus et al., 2000). Therefore, while one might expect that during an episode of, for example, cutting/carving an intense physical pain would occur, this does not happen. Although the mechanisms of this paradox are little known, alterations in the EOS have been proposed as a possible explanation [see for a review: (Bresin & Gordon, 2013)]. Indeed there is a relationship between the EOS, pain and affect processing (Akil et al., 1984), due to shared brain regions (Ribeiro, Kennedy, Smith, Stohler, & Zubieta, 2005; Roth-Deri et al., 2008). Thus, for example, many brain regions involved in the regulation of pain are also implicated in the regulation of emotion and, in turn, are dense in opioid receptors (*e.g.* the ACC) (Ribeiro, et al., 2005; Zubieta et al., 2001). Since the EOS is involved in reward and the regulation of pain and affect, it could mediate the affect regulation effects of NSSI behaviours (Chapman et al., 2006; Sher & Stanley, 2008). Thus, NSSI may increase (a) the activity of μ- and δ- receptors in those individuals who have low resting levels of β-endorphin and enkephalins, or (b) may elicit the release of β-endorphins and enkephalins which could lead to a decrease in negative affect states (or increase in positive affect). Both options lead to a rewarding NSSI effect (Bresin & Gordon, 2013) (see Figure 7A).

Several studies support these hypotheses. For example, using PET methodology, low resting levels of μ-receptors in multiple brain regions (OFC, caudate and nucleus accumbens) have been shown in BPD patients (independently from NSSI behaviours) in comparison to controls. In addition, BPD patients showed a greater activation of the EOS in response to sustained sadness (participants recalled a previously rehearsed past autobiographical vignette associated with sadness) in pregenual ACC, left OFC, left ventral pallidum, left amygdala and left inferior temporal cortex (Prossin, Love,

Koeppe, Zubieta, & Silk, 2010). Stanley et al. (2010) found, in cluster B personality disorder patients (including BPD), that there was an association between lower β-endorphin and enkephalin levels and the presence of NSSI behaviors. This study compared the cerebrospinal fluid levels of endogenous opioids in patients with a history of repetitive NSSI with a diagnostically-matched group of patients who had never engaged in NSSI. Interestingly, these authors elaborated a comprehensive model of EOS and NSSI (see Figure 7B). In another study, Schmahl et al. (2006) found that BPD individuals with NSSI behaviours (compared to healthy controls) presented increased activation in the dorsolateral PFC as well as greater deactivation of the ACC and the amygdala following thermal pain induction. Finally, in a recent study conducted by Niedtfeld et al (2012) in which a negative regulation emotional task and pain induction task were used, alterations in emotion regulation process by means of painful sensory stimulation was evidenced in BPD patients (compared to controls). Concretely, these authors suggest an enhanced negative coupling between limbic (and para-limbic) and PFC regions (inhibitory coupling), when BPD patients experienced pain in addition to emotionally arousing pictures which was not observed in healthy controls (see Figure 7C).

All of the above suggest that two aspects could be very important when trying to understand the affective dysregulatory and non-inhibitory behavior, especially regarding the NSSI behaviours, that characterize BPD patients: (i) the processing of reward/punishment information and (ii) the cognitive control process (including error detection and inhibition). Research in basic cognitive neuroscience has recently provided new paradigms and tools that can inform about the neural dynamics of these cognitive control and emotional regulation processes. This research demonstrates that negative affect, pain and cognitive control activate an overlapping region of the dorsal

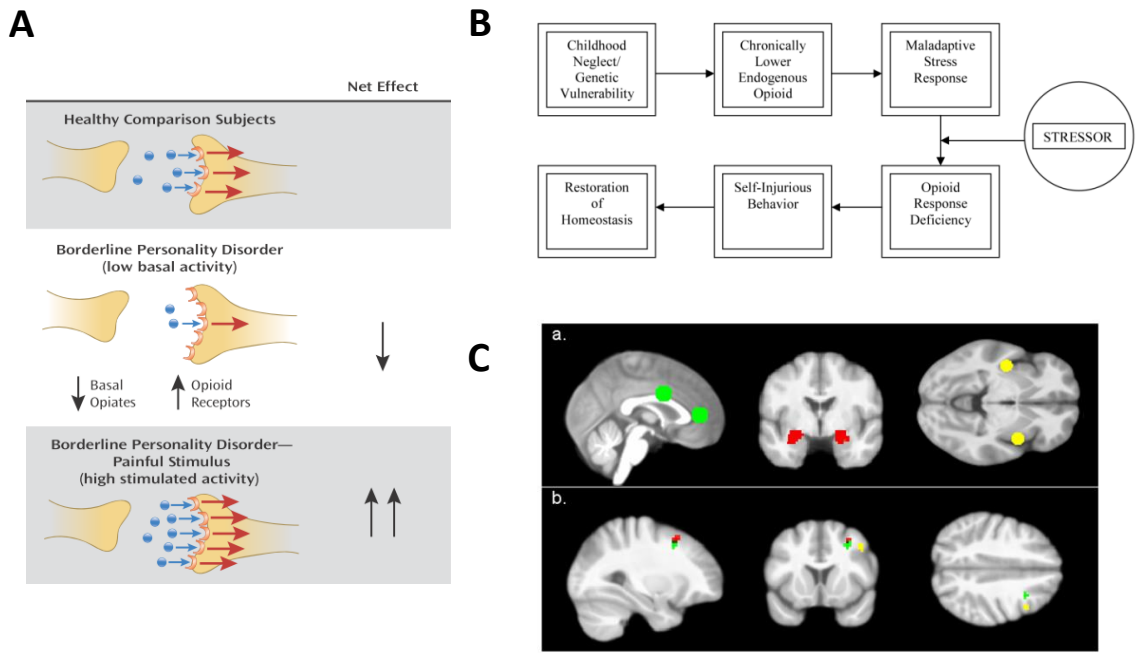


Figure 7. **A**. Basal opioid levels in BPD are hypothesized to be reduced in output, while receptors are increased in number, so that during unstimulated conditions, BPD patients experience dysphoria associated with reduced tonic opioid activity. When stress or pain causes an increase in the release of opioids, there is an increased opioid signal and relief from dysphoria (adapted from: Stanley and Siever, 2009). **B.** Integrated model of NSSI proposed by Stanley et al. (2010) in which opioid deficiency could result from chronic and severe childhood stress and trauma and from a biological predisposition. Chronic stress can lead to a blunted endogenous opioid response to acute stress, and severe physical or psychological traumas may lead to a permanent deficiency state or perhaps habituation of higher levels of endogenous opioids. NSSI behaviours are often associated with the need to feel pain or relieve emotional tension. **C.** Negative co-variation of brain activity between (para-) limbic (*a*) and prefrontal structures when BPD patients experience physical pain during states of enhanced emotional reactivity. It can show a coupling (using a PPI analysis) between the left amygdala (red) and the middle frontal gyrus, the right insula (yellow) and the dorsolateral PFC, and the perigenual ACC (green) and middle frontal gyrus (*b*) (from: Niedtfeld et al., 2012)

cingulate (the anterior midcingulate cortex; BA 24, 25, 32, 33), suggesting a role in the control of these three processes. This brain region constitutes a hub where information about reinforcers can be linked to motor centres responsible for expressing affect and executing goal-directed behaviour. In addition, it synthesizes information about

unlearned reinforcers (for example, pain, predators and threatening conspecifics) and learned reinforcers (for example, aversive cues and negative feedback) with current goals (Shackman et al., 2011).

The next two sections describe the main findings on cognitive control and reward processing, with particular emphasis on BPD.

3. The Reward System

3.1. Description

Rewards are those stimuli that positively reinforce behaviour. Food, water and sexual stimuli are called primary rewards because they reinforce behaviours without having to be learned. In humans, secondary rewards (such as money, warm water or pleasant smells) gain reward value by learned association (McClure & Montague, 2004). The primary rewards, in contrast to the secondary ones, have an innate value and are essential for the maintenance of homeostasis and reproduction. Both kind of rewards present small differences in the brain areas involved in their processing, in spite of their phylogenetical differences (Knutson and Bossaerts, 2007) [see also Figure 9; for a recent meta-analysis: (Sescousse et al., 2013)].

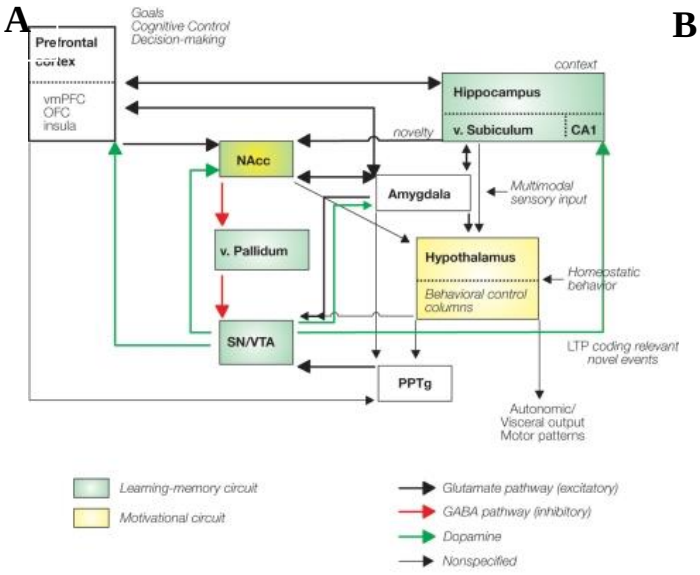
Because, therefore, the reward system is not only involved in the immediate processing of rewards, the association of an event (*e.g.* our actions) with a reward or a punishment (i.e. feedback), but it also constitutes a powerful learning signal, which influences our future decisions. Consequently, the prediction of an error [based on reinforcement learning theory: (Holroyd & Coles, 2002)] is crucial for adaptation as it can be present, for example, in conditioning experiments (Dickinson, 1980) in which an arbitrary stimuli (neutral) will result in a rewarding stimuli (conditioned) after repeatedly presented with a reward object (such as food). Reward system, therefore, is related to a variety of motivated behaviours and cognitive processes, such as reinforcement learning, action monitoring, novelty processing learning, decision making and economic choice or incentive motivation [see for a review: (Camara, Rodriguez-Fornells, Ye, & Münte, 2009)].

Anatomically and functionally, a 'learning loop' of reward processing (see Figure 8A) has been proposed, which is important for encoding predictions based on stimulus-novelty. It involves the hippocampus which sends the novelty signal, through the subiculum, nucleus accumbens and ventral pallidum, to the dopaminergic midbrain regions. Phasic firing on these midbrain neurons increases an association with positive outcomes (and decreases when no reward occurs) which, in turn, results in a release of dopamine in the hippocampus where it might enhance long-term potentiation, leading to memory storage and learning (Schultz, 2002). Dopamine neurons, therefore, do not simply report the occurrence of appetitive events, but also their outputs appear to code for a deviation or error between the actual reward received and predictions about the time and magnitude of the reward (Schultz, Dayan, & Montague, 1997). A second 'motivational loop' (Figure 8A) has been proposed, which allows the organism to seek specific stimuli needed for survival (*e.g.* exploration, reproductive behaviors). It can be activated by specific environmental (internal or external) stimuli and are amplified and energized by affect or emotion. As can be seen in Figure 8A, in these two loops, the nucleus accumbens is a key integrative region which weighs up the different inputs coming from cortical areas (OFC, ventromedial PFC, dorsolateral PFC, insula), limbic regions (amygdala, hippocampus) and the midbrain (sustancia nigra/ventral tegmental area) and therefore modulates the selection of appropriate responses and goal-directed behaviour (Berridge & Robinson, 1998).

A preserved reward system, therefore, is important for adaptation to an environment, above all in changing or/and ambiguous situations or when feedback information is not available. In these situations, at cognitive level, the elicitation of affective responses (emotional valuation), the ability to associate neutral events with the appearance of an emotional-charged outcome (learning) and the ability to store this

information in order to make predictions (memory) are required (Camara et al., 2009). Complementarily, dysfunctional responses to reinforcing stimuli have been proposed as underlying some psychiatric disorders, such as addiction (Hyman, Malenka, & Nestler, 2006; Koob, 2001) or depression (Nestler et al., 2002) among others, as well as several medical conditions (Wang et al., 2001).

Hemodynamic responses associated to reward processing. Neurogimaging studies have evidenced blood-oxygen level dependent activity (BOLD), regarding reward processing, in dopaminergic neurons arising from the ventral tegmental area and projecting onto the ventral striatum via the mesolimbic pathway involving the ACC (see Figure 8A and 8B) [see for a review: (Camara et al., 2009)].



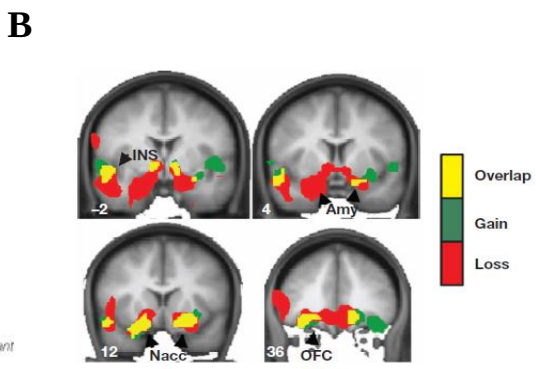


Figure 8. (**A)** Networks involved in the reward processing. Green boxes show the hippocampal-VTA learning-memory circuit. Yellow boxes show the motivational circuit. The direct and indirect projections from the hypothalamus onto the neocortex-limbic structures through the dorsal thalamus are omitted. Figure from Camara et al. (2009). (**B)** Regions that participate in the human reward system after unexpected money gains or losses: the nucleus accumbens (NAcc), Insula (INS), Amygdala (Amy), Orbitofrontal Cortex (OFC). Connectivity between these regions for gains and losses are simultaneously depicted: gain (green), loss (red) and conjunction gain ∩ loss (yellow) (adapted from: Camara et al., 2009). *PPTg:* pedunculopontine tegmentum; *LTP:* long-term potentation; *v:* ventral

In an attempt to distinguish common from specialized reward-related neuroanatomical substrates of multiple rewards, recently, an interesting meta-analysis has been conducted (Sescousse, Caldú, Segura, & Dreher, 2013). It distinguished three separate types of reinforcements –monetary, erotic, food- across which reward processing is assessed using a PET or fMRI methodology. In total, thirty-three experiments on monetary reward, twenty-six experiments on erotic reward and twenty-eight experiments on food reward were included. This meta-analysis supports the idea of a 'common reward circuit' in the brain, because a set of brain regions was consistently recruited by all three reinforcements (although with several spatial differences). These regions are the ventral striatum, the anterior insula, the mediodorsal thalamus, the amygdala and the ventromedial PFC (extending into the pregenual ACC) (see Figure 9).

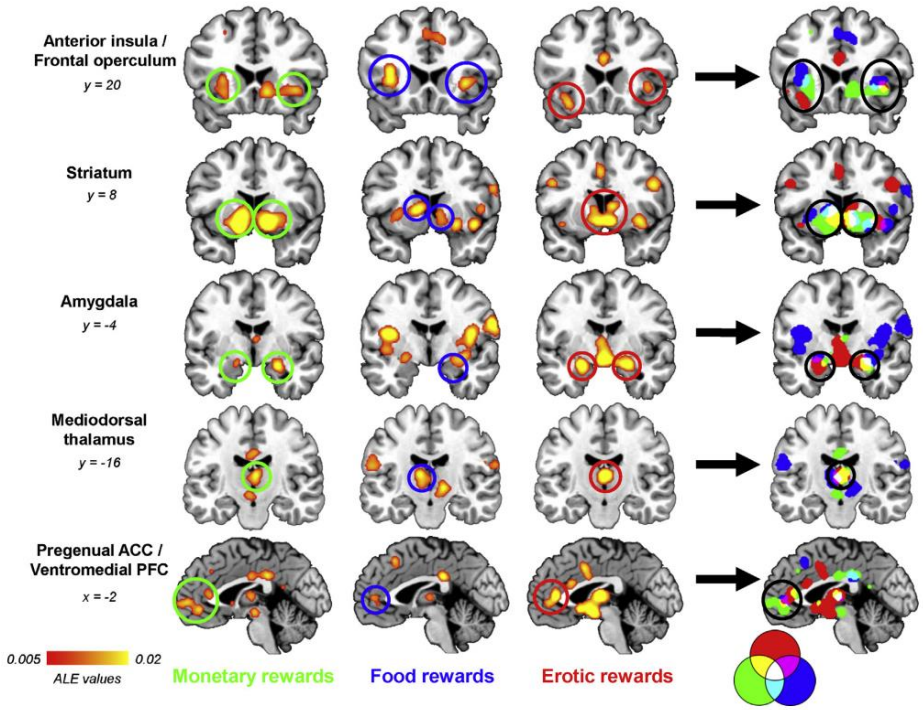


Figure 9. Figure depicts the regions involved in the reward processing of monetary, food and erotic rewards. The ALE[(1)] colour scale shows the values of the magnitudes from meta-analysis (Sescousse et al., 2013), i.e. the degree of consistency across studies. The maps on the right illustrate the overlap of activation clusters across rewards. Figure from Sescousse et al. (2013). [(1)] ALE: Activation Likelihood Estimation

Two of the most relevant areas in reward processing are the striatum (essentially in its ventral part, see Figure 8 and 9) and the ventromedial PFC. The ventral striatum is activated by monetary, food and erotic rewards, but especially by monetary ones. This brain region is part of the limbic loop and receives many projections from the OFC, ACC, the Amygdala and midbrain. Striatum is involved in the integration of cognitive, motor and affective information and, also, influence goal-directed behaviours (Delgado, 2007). Furthermore, the striatum is involved in prediction error as a learning signal (O'Doherty, 2004). The ventromedial PFC is connected to limbic regions and is particularly involved in reward valuation and decision making (Haber & Knutson, 2009; Bechara, Damasio, Damasio, & Anderson, 1994). Especially, right anterior OFC regions show money-specific activations. Both the ventromedial PFC and ventral striatum are involved in the valuation phase in decision-making paradigms (Sescousse et al., 2013).

Other important regions are the amygdala, the insula and the mediodorsal thalamus. The amygdala is interconnected with a variety of cortical regions. It has been proposed that it plays a role in the coding of salience (Météreau & Dreher, 2013) and valence (LeDoux, 2000) of the reward stimuli. The insula is essentially innervated by dopaminergic neurons and is connected with cortical and limbic regions, such as the ventromedial PFC, amygdala or ventral striatum. It is involved in the subjective affective experience of rewards (Sescousse et al., 2013), and plays an important role in the salience processing of such situations as risk and uncertainty (Knutson & Bossaerts, 2007; Preuschoff, Quartz, & Bossaerts, 2008) [for a review: (Nieuwenhuys, 2012)]. Finally, the mediodorsal thalamus is involved in the striatal-thalamo-cortical loop, and mediates between basic reward signals and higher cognitive processes such as

motivation, goal-directed behaviour or reward prediction (Elliott, Friston, & Dolan, 2000; Galvan et al., 2005).

Other regions which showed strong activation in response to only erotic-related stimuli were the hypothalamus and extrastriate body area (Sescousse et al., 2013).

Electrophysiological responses associated to reward processing In humans, electrophysiological (Event-Related Brain Potentials, ERPs) studies have identified several components that specifically indicate the processing of negative outcomes, such as negative feedback, monetary loss, or the detection of performance errors, as well as positive outcomes, such as monetary gains and positive feedback. With regard to negative outcomes, a negative deflection over frontocentral scalp locations known as Feedback-Related Negativity (FRN; also known as Medial Frontal Negativity), has been described as peaking at 250-300 ms after the presentation of feedback in a gambling task (see Figure 10) (Gehring & Willoughby, 2002; Hauser et al., 2014).. The neural sources of this component have been located in the ACC and the posterior cingulated cortex (Müller, Möller, Rodriguez-Fornells, & Münte, 2005). The dynamics of FRN have been explained by reinforcement learning theory [RL theory: (Holroyd & Coles, 2002)], which proposes that when an action produces a *worse than expected consequence* (i.e. an error in a selection task or a loss in a gambling task) there is a decrease in the mesencephalic dopaminergic activity that is transmitted to the ACC [see for a review: (Schultz, 1998)]. This reinforcement learning signal is used to enhance the performance of the task or to increase the adaptation to the present context or situation (Walsh & Anderson, 2012).

In addition, several studies have described an enhancement of theta power activity after negative outcomes, which might not only be related to ACC activity, but also

reflects a broader neural network involved in the orchestrating of adaptive adjustments after errors or negative feedback (see Figure 10 C) (Cohen, Elger, & Ranganath, 2007; Marco-Pallares et al., 2008).

Thus, for example, using a gambling task (see Figure 10 A) in which participants are instructed to bet on two numbers presented on the laptop screen (*e.g.* 25 5), presents negative but not positive feedback (i.e. the current result is different to the previous choice, worse than expected) elicited the FRN (see Figure 1 B). In addition, there are differences between gains and losses in the time frequency activity (see Figure 1 C). Congruently, gain minus loss contrast shows blood oxygen level activation in reward system regions (ACC, ventral striatum and the Insula) (see Figure 10 D).

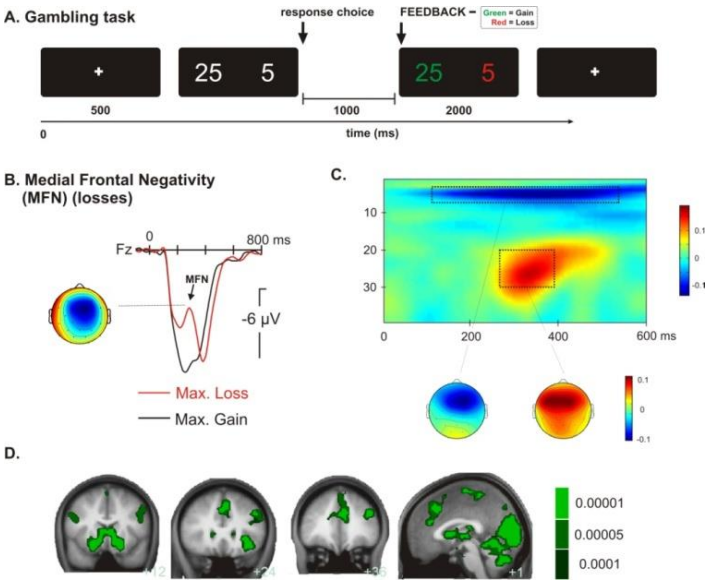


Figure 10. **(A**) Example of gambling paradigm used to evaluate reward processing (William J Gehring & Willoughby, 2002). **(B)** ERPs associated to gains (black line) and loses (red line). Note the increase in the negativity in loses compared to gains. FRN, peaking around 250-300 ms after feedback stimulus. (**C)** Time frequency responses of the gain minus lost contrast. Loses present an increase of activation between 4 and 6 Hz, while gains present an increase in activation between 20 and 30 Hz. (**D)** fMRI brain activations of gain contrast comprising of the ventral striatum, ACC and insula.

Alterations in the feedback processing have been shown in psychopathological conditions such as, for example, depression [larger FRN amplitude than controls (Mies et al., 2011; Santesso et al., 2008)], pathological gamblers [attenuated FRN than healthy controls: (Torres et al., 2013)] or schizophrenia [reduced FRN amplitude: (Morris,

Heerey, Gold, & Holroyd, 2008); but preserved in another study (Horan, Foti, Hajcak, Wynn, & Green, 2012)].

3.2. The Reward system in BPD

In empirical studies, BPD patients present a preference for shorter delays in reward-choice tasks [they choose repeatedly choose a smaller immediate monetary reward than a larger but progressive delayed reward in an impulsive task: (Dougherty, Bjork, Huckabee, Moeller, & Swann, 1999)], showing difficulties inmaking advantageous choices based on previous experience and environmental feedback (Lawrence, Allen, & Chanen, 2010). These impulsive choices are related to the assignment of more value to immediate, short-term rewards (gambling, irresponsible spending, binge eating, substance abuse, unsafe sex, reckless driving) than to long-term rewards (such as safety or security). Congruently, neuropsychological data suggested dysfunctions in response-inhibitory processes and decision making using motivational paradigms (Bazanis et al., 2002; Haaland & Landrø, 2007). Therefore, some common symptoms of BPD show dysfunctional reinforcement processing, such as frequent and risky sexual contacts, high comorbidity with drug addiction, acting out behaviours or anhedonia (see section 1.1.).

In addition, some other findings support a dysfunctional reward system in BPD. Firstly, alterations in the BPD-attachment system have been proposed (Agrawal, Gunderson, Holmes, & Lyons-Ruth, 2004; Steele & Siever, 2010). Rodent models and human neuroimaging have related the attachment system with the reward network via a shared neural circuit which links a neuropeptide-sensitive mechanism (oxitocin/vasopressin), within the anterior hypothalamus, to the ventral tegmental area and nucleus accumbens (Insel & Young, 2001). Therefore, the interaction between these

two systems supports the idea of a dysfunctional reward system in BPD individuals (see Figure 11). Secondly, a dopamine dysfunction in the BPD has been hypothesized (Friedel, 2004), due to the role of dopamine in the impulse and emotion control and cognition. The therapeutic effects of the antipsychotic agents in the treatment of these patients support this idea. Finally, one study commented on above (Prossin et al., 2010) found alterations in the EOS system of the BPD patients.

As indicated, there is a relationship between attachment and reward brain systems, as demonstrated by the findings of both of these studies on maternal and romantic attachment which revealed activity that was not only overlapping to a large extent with itself, but also with the reward circuitry of the human brain (see Figure 11 D) (Bartels & Zeki, 2004). Supporting this relationship, it is noteworthy that when mothers view their own infant's face, in comparison to an unknown infant's face, key dopamine-associated reward processing regions of the brain are activated, including mesocorticolimbic pathways (the tegmental ventral area, ventral striatum and medial prefrontal cortex) and the nigrostriatal pathways (substancia nigra, dorsal striatum and dorsolateral prefrontal cortex) [see Figure 11 A; (Strathearn, 2011)]. In addition, consistently, an insecure adult attachment pattern in BPD patients has been proposed (Agrawal et al., 2004; Fonagy, Luyten, & Strathearn, 2011; Gunderson, 1996). As can be seen in Figure 11A, importantly, there are differences in the brain activity of those mothers with 'insecure' versus 'secure' attachment styles. Thereby, in a fMRI study (Lane Strathearn, Fonagy, Amico, & Montague, 2009) participants classified as 'secure attachment mothers', show greater activation (than 'insecure mothers') of the ventral striatum and medial PFC in response to own-happy infant faces, as well as greater activation of the right ventral striatum in response to own-sad infant faces. In contrast, 'insecure attachment mothers' show greater activation of the right anterior insula. In addition, mothers with secure

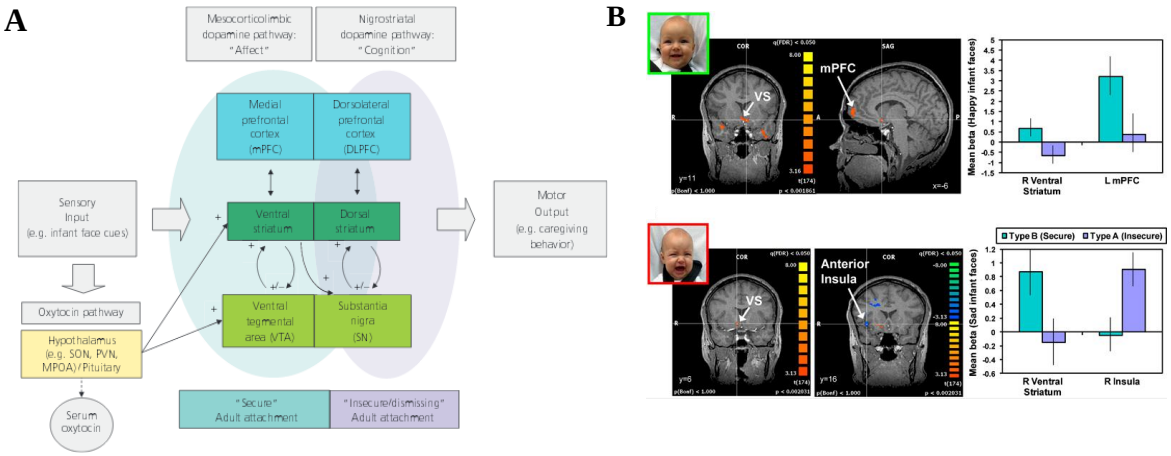
attachment patterns show a greater peripheral oxytocin response during an episode of physical interaction with their infants (see Figure 11 C). These results suggested differences in brain activity regarding the style of adult attachment, which is very important in the case of BPD.

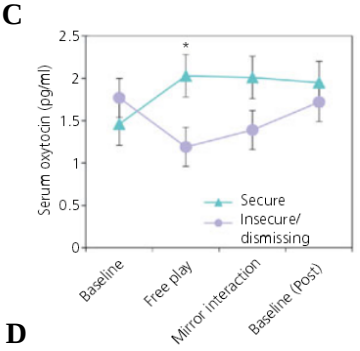
Despite the inherent interest in the study of the reward system in BPD, there is limited scientific literature on this subject. In addition, even though structural and functional resting studies have shown alterations in some of the brain regions involved in the reward processing (see Tables 2, 3 and Figures 8, 10), motivational/reward paradigms have been little used in neuroimaging.

Only two fMRI studies have investigated the reward system of BPD patients. In the first one, Völlm et al. (2007) reported an absence of neuronal responses in the posterior ACC, the caudate bordering to the ventral striatum, and the midbrain including the ventral tegmental area to rewarding outcomes in eight patients with borderline and/or antisocial personality disorder. Most recently, Enzi et al. (2011) investigated the neural interaction between reward anticipation and emotion processing in seventeen BPD females (and seventeen healthy subjects). They used a Monetary Incentive Delay Task in combination with the presentation of emotional pictures (negative, positive or neutral) during the anticipation of reward. Interestingly, this study demonstrated an impact of emotional processing on the reward circuitry since BPD patients were not able to differentiate between reward and 'no outcome' (i.e. no money was either won or lost regardless of whether the subject responded within the required time period or not) when a positive or negative emotional image was presented simultaneously. Thereby, BPD patients showed altered pattern activation in the bilateral posterior ACC and the right para-hippocampal gyrus in the anticipation of both conditions (reward, no

outcome). Furthermore, the BPD patients showed a reduced deactivation of the bilateral ventral tegmental area and the left ventral striatum after a 'no outcome condition', independently of the emotional modulation. These results show alterations in the reward pathways under emotional induction in these patients.

In the same line, a recent ERP study with 18 BPD and 18 healthy controls (Schuermann, Kathmann, Stiglmayr, Renneberg, & Endrass, 2011) showed a reduced FRN-amplitude in BPD patients (relative to controls). In this study, an Iowa gambling task was used. Interestingly, BPD patients made riskier choices than healthy participants and did not improve their performance nor learn during the task. Therefore BPD patients showed a reduced ability to learn from feedback. Interestingly BPD patients showed reduced FRN amplitude following both positive and negative feedback. In summary, this result suggests that BPD patients show a reduced ability to learn from feedback and support the idea of a dysfunctional reward system in these patients.





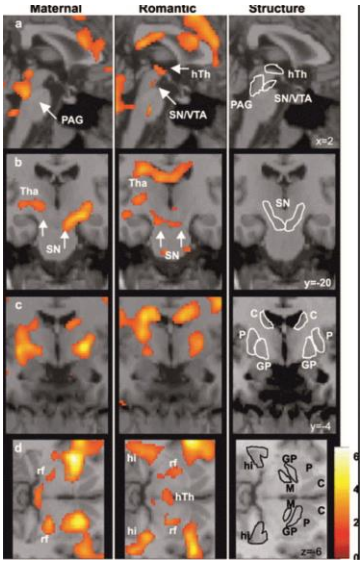


Figure 11. (**A)** Proposed model of dopaminergic and oxytocinergic pathways relating to adult attachment patterns (secure and insecure), from: (Strathearn, 2011). *SON, supraoptic nucleus; PVN, paraventricular nucleus; MPOA, medial preoptic area* (**B)** Brain responses to happy and sad own-infant faces, contrasting mothers with insecure and secure attachment classifications (mean values SEM) On the top, secure mothers show greater activation of the ventral striatum and the medial PFC in response to own-happy infant faces. On the bottom, secure mothers show greater activation of the right ventral in response to own-sad infant faces. Insecure mothers show greater activation of the right anterior insula **(C)** Peripheral oxytocin and related brain activation in response to infant cues. Mothers with secure attachment patterns show a greater peripheral oxytocin response during an episode of physical interaction with their infant. **(D)** Regions that contain a high density of receptors for oxytocin and vasopressin and their overlap with activity related to maternal and romantic love. All labelled regions contain a high density of these attachment related neurohormones in the humans. *C = caudate nucleus; GP = globus pallidus; hi = hippocampus; hTh = hypothalamus; P = putamen; PAG = periaqueductal (central) gray; M = nucleus of Meynert; rf = retrorubal fields/intralaminar/subthalamic nuclei; SN = substantia nigra; Tha = lateral thalamus; VTA = ventral tegmental area;* (a): sagittal, (b,c): coronal, (d): transverse

4. Cognitive Control

In the following section two main aspects of cognitive control will be addressed: (a) executive functions, with special emphasis on metacognition functions, and (b) the processing of errors or conflict-related cognitive control.

4.1. Cognitive control and Metacognition

Executive Functions. Executive function is a broad concept that involves abilities that make independent, purposive, self-serving, and socially responsible behaviour possible (Lezak, 2004; Stuss, 1992). It is an umbrella term that incorporates a collection of inter-related processes, essential for the synthesis of external stimuli, formation of goals and strategies, preparation for action, and verification that plans and actions have been implemented appropriately (Luria, 1976). They have also been defined as a set of inter-related control processes involved in the selection, initiation, execution, and monitoring of cognition, emotion, and behaviour, as well as aspects of motor sensory functioning (Stuss & Alexander, 2000).

Divergent from general cognitive ability or intelligence, executive functioning implies engagement in creative thought, having open-mindedness towards new situations and solutions as well as appropriate self-regulatory skills (Delis et al., 2007). Thus, executive functioning can be considered an important aspect of human experience that may have allowed humans to adapt to changing situations and come up with novel solutions to encountered problems (Barkley, 2001).

The operational definition of Executive Functions, as well as the specific cognitive processes subsumed under this umbrella term, has varied somewhat among authors. For instance, Stuss and Benson (Stuss & Benson, 1984) described their

hierarchical model highlighting important aspects related to the highest levels of cognition such as anticipation, judgment, self-awareness, and decision making. Otherwise, the existence of three major, separable executive functions has been proposed: the 'inhibition' of unwanted responses, the 'shifting' between tasks and mental sets (also called "flexibility"), and the 'updating' (and monitoring of) working memory representations (Miyake et al., 2000). Another influential classification of executive functions proposes, on one hand, 'cool executive functions' which are meta-cognitive in nature. These executive function skills are utilized in abstract contextualized reasoning and have been related with the dorsolateral PFC. These skills are linked with problem-solving competency and require the ability to evaluate a situation correctly, maintain and organize that information in working memory, strategically plan and execute a response, evaluate the efficacy of that response, and make any necessary changes based on the outcome (Metcalfe & Mischel, 1999). On the other hand, there are 'hot executive functions' which have been related with the ventromedial PFC (which is closely connected to the limbic system). These skills are strongly involved with the regulation of affective and motivational processes as well as behavioural inhibition (Zelazo & Müller, 2002).

Therefore, across different models, Executive Functions are responsible for, for example, processes such as: inhibition (i.e. controlling impulses, appropriately stopping one's own behaviour at the proper time), shifting (i.e. solving problems flexibly), emotional control (i.e. modulating emotional responses appropriately). self-monitoring (i.e. attending to one's own behaviour in a social context), initiating (i.e. beginning a task or activity, fluidly generating ideas) or working memory (i.e. holding information in mind for the purpose of completing a task) (Baddeley, 1981). In addition, the conscious capacity to consider who and what we are, what we will value, and how and

when it will be pursued, originates in our self-awareness, has also been proposed as an important process in executive functioning (Barkley, 2012). Therefore, the level of self-understanding and awareness shown by adults with respect to their executive functions is an important factor in gauging the amount of support they will require (see next section: metacognition). Furthermore, other authors have also incorporated social functioning aspects such as the *Theory of mind*, referring to the ability to attribute mental states not only to oneself, but also to others (Hunter & Sparrow, 2012; Stuss, Gallup, & Alexander, 2001).

From an evolutionary point of view, Executive Functions are a set of interdependent, progressively acquired, higher-order cognitive skills that emerge in tandem with the expansion and integration of cerebral, subcortical, cortical, and prefrontal neural networks across early childhood, through adolescence, and into early adulthood (Barkley, 2012; Hunter & Sparrow, 2012).

Despite Executive Functions having been used as a term for the functions of the PFC, they also involve other brain regions. Thus, dorso-lateral PFC has been hypothesized to be primarily engaged in introspective aspects of emotional processing, as well as the identification of and response to internal states (see below for complementary information). The ventro-lateral PFC and posterior PFC have been implicated in rule acquisition, rule switching, inhibition of competing responses and aspects of working memory. The dorso-lateral PFC is involved in planning and response selection in goal-driven behaviour, as well as in spatial working memory. The OFC has been linked to a number of executive skills, including aspects of learning, emotional regulation, cognitive and behavioural inhibition, self-awareness, cognitive flexibility, integration, decision making, working memory, and motivation. On the other hand, the limbic system, particularly the ACC (including pre- and subgenual parts), is implicated

in many aspects of Executive Functions, including emotional regulation and processing, inhibition and direct attention. Additionally, parietal and temporal cortices are involved in aspects of inhibitory control, and in inhibition, shifting, initiating, goal-directed behaviour and working memory respectively. Finally, the cerebellum has been related with motor control and emotional processing [see for brain regions involved in Executive Functions: (Barkley, 2012; Baron-Cohen et al., 1994; Cummings, 1993; Hunter & Sparrow, 2012; Petrides, 1994; Shing, Lindenberger, Diamond, Li, & Davidson, 2010); see also Figure 12A).

Ultimately, in a social and constant changing world, a correct executive functioning facilitates a proper self-regulation. It refers to the process by which people initiate, adjust, interrupt, stop, or otherwise change thoughts, feelings, or actions in order to affect realization of personal goals or plans or to maintain current standards (Carver & Scheier, 2001; Heatherton & Vohs, 2000; Heatherton, 2011). In contrast, problems in executive functioning lead to failings in self-regulation. In this scenario people could become impulsive, emotional wrecks, lashing out upon the smallest provocation, blurting out the first thing that comes to mind, and engaging in whatever behaviour feels good at the time (Heatherton & Wagner, 2011). Thus, for example, damage to ventromedial PFC, lateral PFC, and ACC (including pre- and subgenual parts; see Figure 11 A) (Heatherton, 2011) has been associated with problems in planning, difficulty in carrying out goal-directed behaviours (Cohen, Kaplan, Moser, Jenkins, & Wilkinson, 1999), or problems in the execution of real-world tasks such as following a shopping list (Barceló & Knight, 2002). In addition, specific ventromedial PFC damage often results in a deficiency in incorporating feedback from others (and social norms) to make appropriate behavioral choices or adjustments in certain social contexts, resulting in social disinhibition and inappropriate approach behaviour toward

other individuals (Beer, John, Scabini, & Knight, 2006). In a similar vein, difficulties in emotional self-regulation can appeared due to a failure in top-down regulation of the amygdala by the PFC brain regions (Ochsner et al., 2004; Ochsner, Bunge, Gross, & Gabrieli, 2002) (see also section 1.5.2. for several examples of emotional paradigms and studies with the BPD population; see Figure 12A).

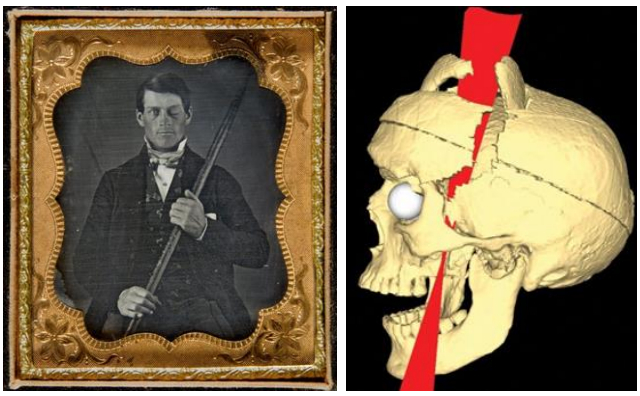


Figure 11. Photo of Phinias Gage, after the accident, showing the iron rod which damaged his PFC (left). Reproduction of the accident (right), in which a large iron rod was driven completely through his head, destroying much of his brain's left frontal lobe.

One prototypic example of PFC damage is the famous case of Phineas Gage (see Figure 11), the railroad foreman who suffered a tamping iron through the head in a work-related accident, leading to dramatic personality changes, with disinhibition and often inappropriate behaviour as well as severe loss of motivation in the absence of any observed cognitive impairment (Macmillan, 2000).

Metacognition. Metacognition has been both broadly and vaguely defined in literature, when referring to higher-order self-reflective cognitive processes that may be used for regulating information processing (Flavell, 1979; Fleming & Dolan, 2012; Lysaker et al., 2005; Metcalfe & Shimamura, 1996; Nelson & Narens, 1994; Shimamura, 2000; Yeung & Summerfield, 2012; Zimmerman & Schunk, 2011). Metacognition essentially means cognition about cognition; that is, thoughts about thoughts, knowledge about knowledge or reflections about actions, therefore, it refers to the capacity to reflect upon and evaluate cognition and behaviour (Flavell, 1979). This

kind of introspection is crucial for making good decisions in every-day situations such as ‘do I want to go out tonight?’, ‘will I enjoy myself?’, ‘is my aim accurate?’, ‘how sure am I that I'm right?’ or ‘is that really the correct answer?’.

According to the widely accepted conceptualization (Nelson & Narens, 1994), two central dimensions of procedural metacognition, that is, monitoring (i.e., performance predictions: judgments-of-learning; performance postdictions: confidence judgments) and controlling (i.e., error correction) enable a continuous exchange of information between the object-level (the task at hand) and the meta-level (a representation of the task at hand and its mastery). The role of the meta-level (i.e. metacognition) is to evaluate object-level activations and, based on this evaluation, initiate feedback control. Thus, for example, memory evaluations such as *judgments of learning* (e.g., ‘‘how well did I learn the material?’’) or *feelings of knowing* (‘‘how well will I perform on a test of the material?’’), can be construed as aspects of metacognitive monitoring.

To the extent that metacognition imposes top-down regulation of information processing, this concept is centrally linked to aspects of executive/cognitive control. Therefore, the ability to use environmental signals in such a flexible manner is part of high-level metacognitive executive functions, which include planning, problem solving, working memory, and performance monitoring (Burgess, Veitch, de Lacy Costello, & Shallice, 2000; Damasio, 1995; Grafman & Litvan, 1999; Stuss, Shallice, Alexander, & Picton, 1995). In addition, metacognition is also important for guiding self-regulatory learning (Ridley, Schutz, Glanz, Weinstein, & Taylor, 2011; Winne, 1996).

It is assumed that individual differences in Executive Functions may be related to metacognitive control, because both groups of processes are executive in nature [i.e.

planning, evaluating, and regulating strategies; see: (Best & Miller, 2010; Fernandez-Duque, Baird, & Posner, 2000)]. Moreover, Executive Function skills and metacognitive monitoring seem to share an individual's ability to reflect and evaluate their own performance (i.e., self-perception or self-concept), relying on the ability to introspect, that is, to form and activate mental representations about oneself that take both past and ongoing activities as their content (Lyons & Zelazo, 2011). In reference to this, therefore, metacognitive knowledge includes knowledge of general strategies that might be used for different tasks, knowledge of the conditions under which these strategies might be used, knowledge of the extent to which these strategies are effective, and knowledge of *self* (Flavell, 1979; Pintrich, 2002).

Regarding the above, for example, individuals who are better at making accurate performance predictions or who are better at estimating the correctness of provided answers, typically control more efficiently their actual behaviour (*e.g.*, they allocated the proper time needed to study something), and/or detect and correct more errors or comprehension difficulties (Koriat & Goldsmith, 1996). In addition, notice that self-perceived competence and metacognition knowledge are inter-related (see below) (Kleitman & Stankov, 2007). For instance, availability heuristics explain how individuals assumed to estimate the frequency of a specific event, or the likelihood of its occurrence, 'by the ease with which instances or associations come to mind' (Kahneman & Tversky, 1979). In this vein, feelings of knowing can be subjected to cognitive bias and, for example, people reported more commission than omission errors (*e.g.* in the Wisconsin Sort Carting Test) when they were asked to rate it (even when omission errors supposed misinformation). Similarly, overconfidence in a certain task is liable to lead to premature cessation of problem-solving efforts, insufficient checking of memory retrieval (resulting in poorer performance than might otherwise be achieved)

faulty assessment of the difficulty of problems for other people due to hindsight biases, insufficient study, and an inappropriate and self-defeating lack of perseverance under difficult cognitive conditions (Castel, McCabe, & Roediger, 2007).

Regarding the neural bases of metacognition, abundant research has implicated the PFC in top-down control information processing (Fernandez-Duque et al., 2000; Pannu & Kaszniak, 2005; Stuss, Gallup, & Alexander, 2001). In face of the 'dynamic filtering theory' (Shimamura, 2000), the PFC with its extensive projections to and from many cortical regions, regulates posterior cortical circuits by way of a filtering of gating mechanisms. Therefore, the PFC selects appropriate -and suppresses inappropriate- environmental signals.

Self-referential information processing and metacognition. One aspect closely related to metacognition is the proper processing of information of the Self (who we are). The Self is a multi-facet construct (Damasio, 1995; Gallagher, 2000, 2013), which can be separated in two main aspects: (a) the self as an experiencing subject (i.e. "me", the consciousness of oneself as an immediate subject of experience) and, (b) the self as object of knowledge (i.e. "I", the representation and evaluation of one's personal characteristics and experiences) (Damasio, 1999; Gallagher, 2000; Legrand, 2007). The experience of self as the object of attention is the psychological state known as self-awareness, which encourages people to reflect on their actions and understand the extent to which those actions match personal values and beliefs as well as group standards (similar to the concept of metacognition) (D'Argembeau, 2013; D'Argembeau et al., 2013). In addition, regarding the self as an object involve the ability to recognize one's physical appearance, representations of one's personality traits and other personal attributes, as well as memories of one's past experiences and knowledge of facts about one's own life (Klein & Lax, 2010; Renoult, Davidson, Palombo, Moscovitch, &

Levine, 2012). Interestingly, these two parts of self (experiencing *versus* object) are dissociable (one component can operate independently from another) which makes possible, for example, that the knowledge of one´s personality traits is functionally independent from memories of one's past experience (Klein, Robertson, Gangi, & Loftus, 2008).

In this vein, importantly, some authors have differentiated between 'self-related' and 'self-relevant' information processing (Northoff & Hayes, 2011; Northoff et al., 2006). Despite both types of information being salient, they have been related to different brain regions (Schmitz & Johnson, 2007), referring self-relevant information to a most broader category (*e.g.* 'my car'). For instance, a task in which participants were encouraged to appraise how they feel (pleasant, unpleasant, or uncertain/neutral), while viewing negative, positive, and neutral valence images, is a self-referential task which evoked a dorso-medial PFC, dorsorostral ACC and posterior cingulate cortex responses (Gusnard, Akbudak, Shulman, & Raichle, 2001). In Figure 12B, the consistent activation of these regions across different studies can be seen. In contrast, a gambling task in which participants were asked to bet on different coloured squares and, consequently, they received a coin with a monetary value, this is an example of a self-relevance task. In this case, ventro-medial PFC, limbic and paralimbic brain regions were activated and modulated by the presence of gains (Elliott, Newman, Longe, & Deakin, 2003).

Self-related beliefs serve the metacognitive function of interpreting momentary events and experiences and constitute beliefs about self-efficacy which, in turn, play a major role in whether or not people are motivated and able to adopt and follow systematic metacognitive strategies. Thus, people who are low in self-efficacy are easily discouraged by challenges and failures, and they tend not to apply appropriate self-

regulatory goals (Akama, 2006). Metacognitive beliefs may be momentary convictions, like the 'on the tip of the tongue' phenomenon or the 'feeling of knowing', or they may be more enduring beliefs, such as the intuitive theories that people hold about intelligence and learning. Enduring beliefs about domain-specific self-confidence may be just as important, metacognitively speaking, as momentary estimates of self-confidence (Nelson & Narens, 1994).

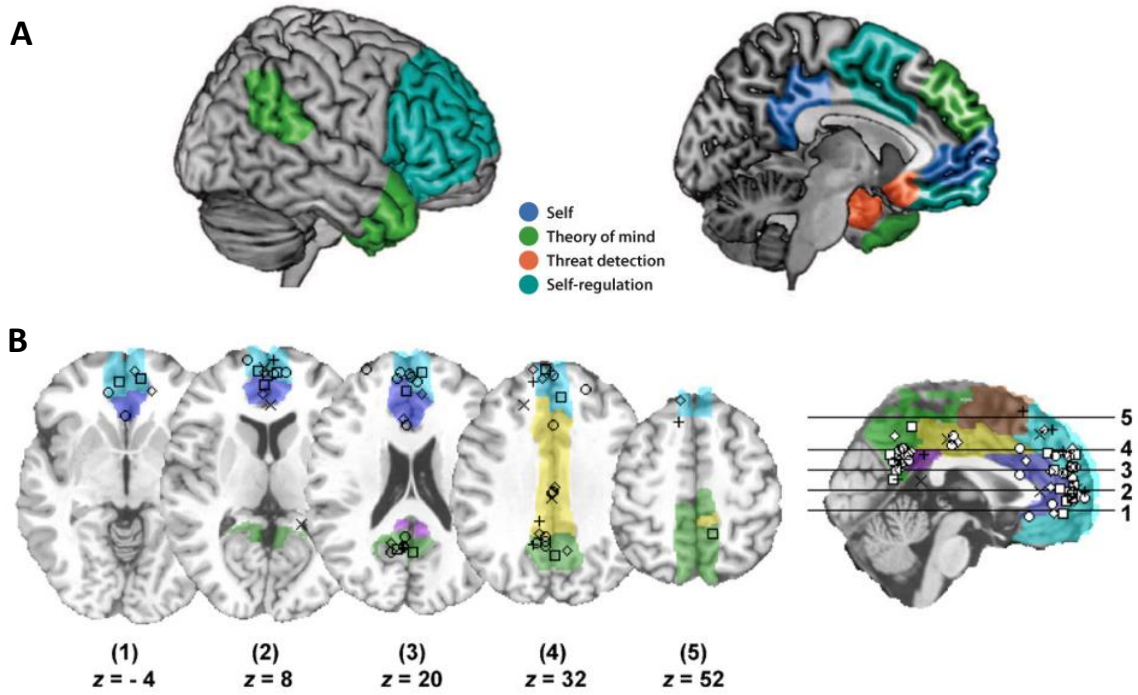


Figure 12. **(A)** Brain regions commonly associated with studies of self (blue), theory of mind (green), threat detection (orange) and self-regulation (dark green). From: (Heatherton, 2011) **(B)** Loci of statistically significant activation (as reported by individual papers) resulting from multiple neuroimaging task domains that require self-referential introspection of stimuli. Squares = appraisal of one's own personality traits; Circles = appraisal of personal morals, opinions, attitudes, and aesthetics; Diamonds = personal reaction to affective stimulus content; Exes = appraisal of one's own visuospatial perspective; Crosses = appraisal of personal preferences. From: (Schmitz & Johnson, 2007)

To summarize, proper self-awareness requires self-correcting referential information processing. To date, numerous studies have examined brain regions that are

involved in processing information about the self compared to those associated with processing semantic information more generally or processing information about other people, with the vast majority finding heightened activity in the ventral medial PFC, the posterior cingulate cortex, and the precuneus (D'Argembeau, 2013; Northoff et al., 2006; Schmitz & Johnson, 2007) (see Figure 12B). Besides, patients with lesions in these regions show significant impairment in their ability to engage in self-reflection and introspection (Beer, Heerey, Keltner, Scabini, & Knight, 2003; Wheeler, Stuss, & Tulving, 1997).

Assessment of Executive Functions and Metacognition. In the assessment of executive functioning, standard neuropsychological tasks are commonly used in neuropsychological studies for inferring cognitive impairment in daily executive functions (*e.g.* Stroop test). Nevertheless, there is an ecological limitation of laboratory-based measures for this purpose (Burgess, Alderman, Evans, Emslie, & Wilson, 1998). This limitation is present in BPD studies, as pointed out in a previous section (BPD-neuropsychology section). For instance, results of a recent meta-analysis indicate that the relationship between self-reported and behavioural measures of impulsivity is small (Cyders & Coskunpinar, 2011). This work, which analyzed twenty-seven studies, found a slight overlap between these two types of impulsivity measures (an effect size of only .097).

Current performance-based tests are constructed to measure individual components of Executive Functions over a short time frame, not the integrated, multidimensional, relativistic, priority-based decision-making that is often demanded in real-world situations. In this line, notice that a person may be able to gather sufficient cognitive resources to perform Executive Funtion tasks for a brief period, but the

exertion cannot be sustained over the duration of daily activities. In addition, Executive Functions laboratory tasks assume that they are divided into 'cubby holes' (each with its own label) however, contrarily, this rarely occurs outside a laboratory environment, when assessing real people's real-life performances. Furthermore, importantly, Executive Functions may vary according to setting, and for feelings such as fatige, pain, stress or mood (Arnsten, 1998; Mitchell & Phillips, 2007).

To improve the ecological validity of executive tests, the addition of functioning and adaptive scales to the traditional tests in the assessment has been proposed on brain damaged patients (Chaytor, Schmitter-Edgecombe, & Burr, 2006). Others, have developed ecological-Executive Function tests for measuring behaviour such as the 'behaviour rating inventory of executive function (BRIEF)' (Isquith, Gioia, & Espy, 2004), which has been mainly used on children with learning disabilities and traumatic brain injury patients (Gioia & Isquith, 2004). Interestingly, a recent report found that the BRIEF was more highly correlated with parent and teacher description of impairment than with performance in laboratory tests of Executive Functions (McAuley, Chen, Goos, Schachar, & Crosbie, 2010), suggesting that it may be an appropiate standardized tool for capturing real-world data on a person's Executive Functions. Interestingly, this inventory incorporates items concerning daily activities and provides the option of a complementary form addressed to relatives. Importantly, several authors have proposed that ecological ratings of dysfunction may require complementary information from relatives or close friends who had '*in vivo' life experiences* with the patient (Parker et al. 2004). Because awareness of the integrity of own Executive Functions can vary among both healthy individuals and those with a variety of illnesses, an informant's report on the same executive functions provides an empirical basis from which to begin indentifying problems of awareness. Using this methodology, interestingly,

discrepancies between self- and others- information in a wide range of personality measures have been shown (Klonsky, Oltmanns, & Turkheimer, 2002; Oltmanns & Turkheimer, 2002).

Self-assessment of cognition is an interesting field of study for cognitive neuroscience. Here, a crucial variable of interest lies in the accuracy of metacognitive reports with respect to their object-level targets; in other words, *how well do we know our own minds*. In healthy individuals, performance of a particular cognitive task and metacognition of performance are usually tightly coupled (to be precise, metacognitive accuracy) (Schwartz & Metcalfe, 1994). Contrary to this, in cases of traumatic injury to the frontal lobes individuals may have deficits in self-knowledge of altered cognition and personality, as measured by the discrepancy between reports from the patient and family members (Schmitz, Rowley, Kawahara, & Johnson, 2006). To the extent that the meta-level imperfectly monitors the object level, self-reports about cognition will be inaccurate, perhaps manifesting themselves as a lack of awareness of the object level (Schooler, 2002). Following this reasoning, accurate mental representations of the self, specifically in regard to personal traits and daily abilities, depend on the level of congruency between one's actual neurobehavioural status and one's self-appraised notion of this status. Therefore, high congruence will favour both goal-directed and self-regulatory behaviour, and is thus better attuned to what others may observe (Schmitz et al., 2006).

Importantly, PFC damage selectively affects the accuracy of metacognitive reports while leaving task performance relatively intact. For instance, disrupting dorsolateral PFC using trans-cranial magnetic stimulation decreases metacognition without affecting task performance (Rounis, Maniscalco, Rothwell, Passingham, & Lau, 2010). Interestingly, this impairment was only witnessed when following correct but not

incorrect decisions, suggesting a PFC-role in representing confidence rather than monitoring for errors (this capacity is linked with other brain regions: see next section). Indeed, accurate metacognitive commentaries about performance require access to information about both beliefs (confidence) and responses.

4.1.1. Metacognition and psychopathology

In recent years, clinicians in the fields of mental health have been increasingly interested in how persons with psychiatric conditions experience a range of difficulties related to how they think about themselves and others (Dimaggio, Salvatore, Popolo, & Lysaker, 2012). In this field of study, researchers have commonly and indistinctly used metacognition and mentalization (i.e. the capacity to conceive of one's own and others' mental states (Allen & Fonagy, 2006).

Metacognition (dis)abilities are strongly associated with many forms of adult psychopathology (Lysaker et al., 2005). Importantly, in schizophrenic patients (similar to what happens in BPD), heterogeneous results have been obtained by studies exploring the functional impact of cognitive deficits, suggesting that there is no direct relationship between these two aspects. One proposed explanation is that metacognition may play an intermediate role in moderating the link between cognitive deficits and functional impairment (Quiles, Prouteau, & Verdoux, 2013). In this line, several studies have reported that metacognitive difficulties strongly interfere with social functioning and have predicted more community functioning in persons with schizophrenia than cognitive deficits (Tas, Brown, Esen-Danaci, Lysaker, & Brüne, 2012). Metacognitive skills may hence be viewed as a key factor in translating cognitive performance skills in daily life.

From a psychological perspective, biases in self-information processing are a source of suffering (Beck et al., 2006; Clark & Beck, 2010). For this reason, dysfunctional beliefs about cognition (which constitute metacognition), are the basis for the development and maintenance of clinical problems (Matthews & Wells, 2000; Wells & Matthews, 1996), due to, as mentioned previously, this guide's information processing. For instance, in a study about ruminative thinking in depression (Papageorgiou & Wells, 2003), which has been found to be linked to distorted interpretations of live events (augmenting pessimism about positive events in the future and poor solutions to interpersonal problems) (Lyubomirsky & Nolen-Hoeksema, 1995), authors showed that perseverative negative thinking has multiple effects on low-level and strategic cognitive operations required for restructuring self-knowledge and developing effective coping strategies. Thus, negative beliefs and appraisals of coping (i.e., negative "on-line processing") contribute most proximally to emotional disturbance.

Metacognition and BPD. The term metacognition has been little used in BPD research [*see for instance:* (Judd & McGlashan, 2008; Semerari et al., 2005]. In line with the above reasoning, BPD patients are highly vigilant for negative stimuli, especially when stimulus are associated with negative self-appraisals (*e.g.* using the emotional stroop task) (Sieswerda, Arntz, Mertens, & Vertommen, 2007). Importantly, they also experienced attenuated inhibition of negative emotional stimuli shown by a poor performance during negative priming, directed forgetting, and a linguistic go/no-go task (Domes, Winter, Schnell, & Vohs, 2006; Silbersweig et al., 2007). Furthermore, BPD patients have difficulties engaging brain prefrontal areas when employing psychological distancing to regulate negative emotions (Koenigsberg et al., 2009). In addition, in an interesting study (Schulze et al., 2011), researchers used a reappraisal

paradigm in which, first, BPD participants viewed a picture (aversive) on the screen and, after this emotional induction, a single word instruction was presented asking participants to 'maintain', 'increase', or 'decrease' their initial emotion. Importantly, BPD patients showed difficulties in the cognitive reappraisal of aversive stimuli (i.e., negative pictures), which are associated with attenuated orbitofrontal activity along with enhanced bilateral insula activity. Therefore, they showed deficits in being capable of voluntarily decreasing aversive emotions by means of cognitive reappraisal. This result, importantly for the present dissertation, suggests impairment in metacognition, in particular in those metacognitive control skills (see Figure 13A).

Complementarily, it has been demonstrated that mindfulness training can facilitate the reappraisal of stressful events and distressing thoughts (Chiesa, Serretti, & Jakobsen, 2013; Garland, Gaylord, & Park, 2009). This training promotes the awareness of all emotional and cognitive events as they occur in the present, a concept clearly related to metacognition. Therefore, as can be seen in Figure 13B, it allows one to "decenter" (*i.e.* 'step outside of one's immediate experience, thereby changing the very nature of that experience') from the primary, or initial, stress appraisal. As well as this, it facilitates reappraisal with a different perspective that can promote more positive attributes. Thus, this metacognitive approach to mindfulness promotes a shift in mental processes (second order) rather than a direct change of the mental content or behaviours (first order). This shift in perspective (stance) enhances self-regulation and promotes an adaptive *response* (action), rather than maladaptive stress *reactivity* (reaction). Importantly, mindfulness has been a useful intervention with BPD patients, suggesting that their problems in self-regulation are, at least in part, related with metacognitive impairment (Linehan, 1993; Soler et al., 2012; Stoffers et al., 2012).

Another focus of study has been the autobiographical memory (see also section 1.5.2.). It refers to memories of one's personal life and plays a major role in identity and emotion regulation (Dimaggio et al., 2012). Importantly, autobiographical memory (that is self-referential information) and metacognition are closely related due to having shared brain regions (Rabin & Rosenbaum, 2012; Spreng & Grady, 2010). Interestingly, several studies have shown alterations in the autobiographical memory of BPD patients. Thus, for example, in a fMRI study (Schnell, Dietrich, Schnitker, Daumann, & Herpertz, 2007), during the recall of autobiographical memories, BPD subjects showed a deficit of selective activation of areas involved in autobiographical memory retrieval (they activated the same brain areas both in aversive and neutral memories) suggesting a general tendency towards a self-referential mode of information processing in BPD, or a failure to switch between emotionally salient and neutral stimuli.

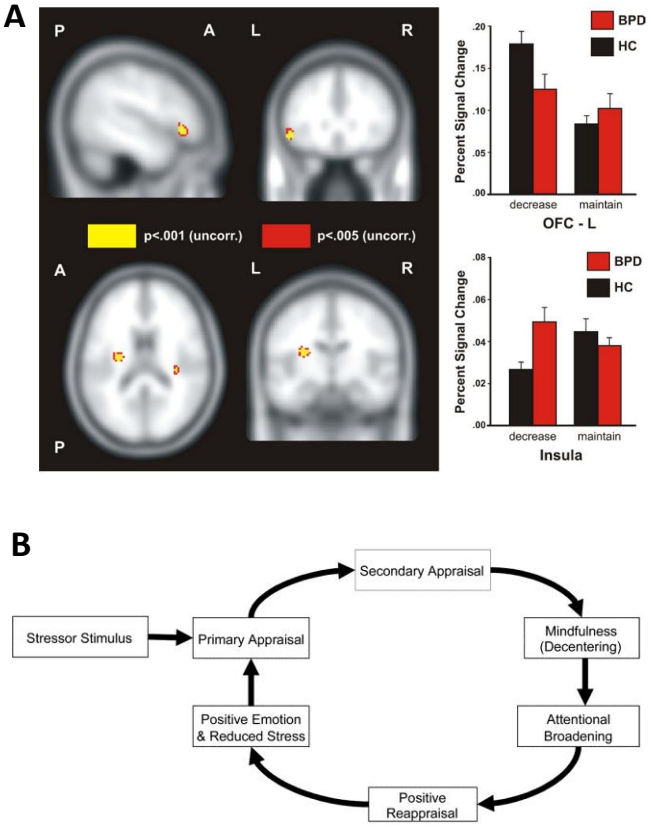


Figure 13. **(A)** The left OFC demonstrated enhanced activity during the decrease of the initial emotional response for the healthy control (HC) compared with the BPD group, accompanied by dampened activation of the bilateral insula in the healthy control group but not for borderline personality disorder patients. *A = anterior; L = left; P = posterior; R = right.* Reproduced from: (Schulze et al., 2011). **(B)** Mindfulness process. Reproduced from: (Garland et al., 2009)

These findinsg, in addition, fit well with the mentalization-based approach to BPD (see section 1.2.). Briefly, this perspective proposes that self-awareness is built in the context of social attachment. BPD patients show insecure attachment style, leading to mentalization failures. During the mentalization-based treatment, a core aspect is to help patients to narrate specific autobiographical memories, suggesting that its enrichment may promote improvements in metacognitive capacity (Bateman & Fonagy, 2004).

In this context, finally, BPD patients usually present a lack of insight or unawareness of illness, experience difficulties describing their own emotions, and in seeing their own thought processes in a detached and reflective way (Semerari et al., 2005); all these could be conceived of as a failure in metacognition.

4.2. Error detection and inhibition

Error processing, which is also referred to as "response monitoring" or "performance monitoring", involves detecting errors during a task performance and adjusting behaviour accordingly. Thus, a preserved error-processing is critical for adjusting behaviour to optimize outcomes.

4.2.1. Behavioural indexes of error processing

One index of error-processing is the response inhibition that is the suppression of pre-potent but contextually inappropriate response. Traditionally, several tasks have been used in order to capture this process, such as the go no-go paradigm, the Stroop or the Eriksen flanker task (Eriksen & Eriksen, 1974). Another behavioural index is the ability for correction of errors in the short-term, that consist of trial-by-trial adjustments, which include the immediate self-correction of errors and the slowing of reaction time

(RT) in trials that follow an error (post-error slowing: PES; see Figure 14) (Rabbitt, 1966).

It is noteworthy that errors in a behavioral task are both salient (unexpected) and aversive, therefore, a failure in the performance have negative consequences. The Reinforcement learning theory allows us to understand how the short-term behavioural adjustments after the commission of an error, can result in long-term behavioural changes (Holroyd & Coles, 2002).

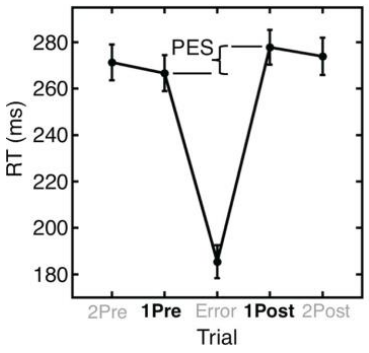


Figure 14. Graphical representation of Post Error Slowing (PES). The Abcissa axis shows the previous and following trials to error one. The Ordinate axis shows the reaction time (RT). As can be seen, increased RT appears after an error. Image from Manoach et al (2013).

4.2.2. Neurophysiological indexes of error processing

Error Related Negativity (ERN). The ERN or error negativity (Ne) is an ERP component that peaks 80-100 ms after the commission of an error in a speeded action-selection task (Figure 15) (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1990; Gehring, Goss, Coles, Meyer, & Donchin, 1993). The ERN is defined usually as the peak of the difference between the averaged waveforms of error- and correct- trials which are time-locked to the onset of the response. The ERN is the earliest error marker and is "generic" because it occurs in a wide variety of speed-response tasks involving a variety of stimuli (*e.g.* visual, auditory) and responses (*e.g.* manual, vocal) (see for a review: Manoach & Agam, 2013).

While the first interpretations related this component to error commission (Gehring et al., 1993), latter accounts related it with reinforcement learning (Holroyd & Coles, 2002; Holroyd et al., 2004; Paus, Petrides, Evans, & Meyer, 1993). The ERN amplitude is greater when accuracy is emphasized over speed (Gehring et al., 1993), when errors are corrected (Scheffers & Coles, 2000) and when errors are less expected (Gehring et al., 1993; Hajcak, McDonald, & Simons, 2003). Additionally, a larger ERN is associated with greater post-error slowing of responses (Debener et al., 2005) suggesting that it contributes to the dynamic of the trial-by-trial behavioural adjustments of performance.

The generators of ERN have been located in the ACC (Holroyd, Dien, & Coles, 1998), with contributions of the PCC (Agam et al., 2011). Therefore, alterations in the ERN have been reported in individuals with ACC lesions (Swick et al., 2008), and fMRI studies of errors have shown error-related ACC activity (Kiehl, Liddle, & Hopfinger, 2000). Complementarily, studies with monkeys support the involvement of ACC in error potentials (Gemba, Sasaki, & Brooks, 1986). The dynamics of the ERN (Holroyd et al., 1998; Holroyd et al., 2004) is based on the fact that immediately after an error, the striatum detects a mismatch between the intended (correct) versus actual (error) outcome, causing a phasic decrease in mesencephalic dopamine release that results in the disinhibition of neurons in the ACC.

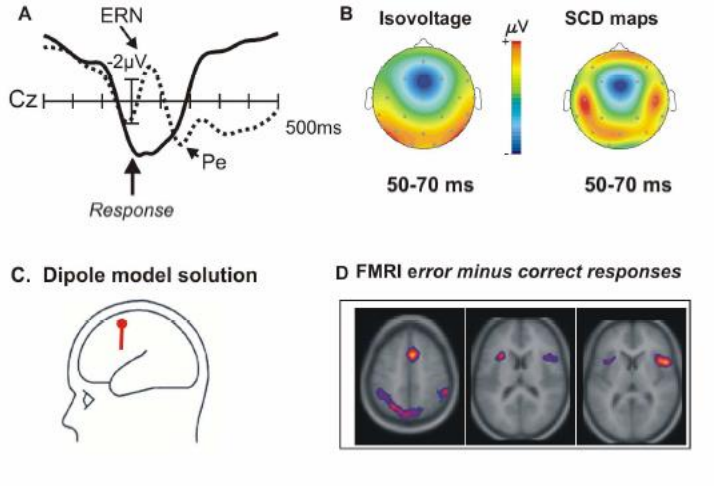


Figure 15. **(A)** ERP components associated with correct and erroneous responses [ERN and Pe (see below)]. The component peaks 60 ms after the commission of the error [data from: (Rodriguez-Fornells, Kurzbuch, & Münte, 2002)]. (**B)** Topographical maps which show a clear frontocentral distribution of the ERN component. (**C**) Neural source localization of the ERN component in the ACC. **(D)** fMRI study showing the main regions activated when an erroneous response is produced (ACC, bilateral insular cortex and right inferior frontal gyrus (Marco-Pallarés, Camara, Münte, & Rodríguez-Fornells, 2008).

Error Positivity (Pe). In the response-locked error-trial waveform, the error positivity (Pe) (van Veen & Carter, 2002) appears usually following the ERN, this is 300-500 ms after an error [see for a review: Overbeek, 2012] (see Figure 15). The Pe generation has been located in the rostral ACC (van Veen & Carter, 2002). Unlike the ERN, the Pe is present only for perceived errors being related with error awareness and, probably, reflecting an affective response to the error (Endrass, Reuter, & Kathmann, 2007; Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001). In addition, the Pe has been associated with short-term performance adjustments such as error correction and post-error slowing (Nieuwenhuis et al., 2001).

4.2.3. Error processing in Psychiatry

Failures in error-processing have been associated with psychopathology. Indeed, increased ERN amplitude has been shown in anxiety disorders (Gehring, Himle, & Nisenson, 2000; Santesso, Segalowitz, & Schmidt, 2006) and depression (Holmes & Pizzagalli, 2008), which suggest that these patients are more sensitive to errors. In

contrast, impulsivity disorders have shown a decreased ERN and Pe amplitude compared to controls (Franken, van Strien, Franzek, & van de Wetering, 2007; Ruchsow, Spitzer, Grön, Grothe, & Kiefer, 2005; van Meel, Heslenfeld, Oosterlaan, & Sergeant, 2007), suggesting poor adaptive control in base of error-processing learning. In addition, other mental conditions such schizophrenia have also shown reduced ERN and Pe amplitude (Foti, Kotov, Bromet, & Hajcak, 2012).

Despite all these findings, some data is inconclusive and contrary in some cases (see Figure 16 A).

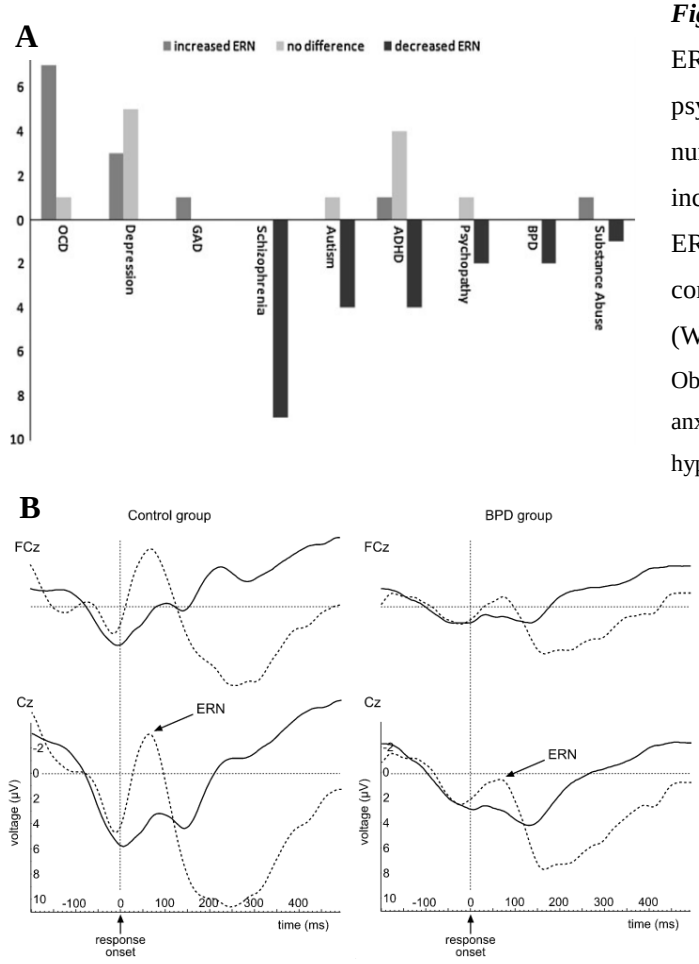


Figure 16. **(A)** The bar graph represents the ERN component alterations in relation with psychopathology. The Y-axis shows the number of studies which reported increased/decreased or no difference in the ERN amplitude relative to the healthy control group. Graph from Weinger et al (Weinberg, Riesel, & Hajcak, 2012). *OCD*: Obsessive-compulsive disorder; *GAD*: General anxiety disorder; *ADHD*: Attention deficit hyperactivity disorder. **(B)** Grand average response-locked waveforms for correct and incorrect responses for the control (left) and the BPD (right) groups. Central electrodes FCz and Cz are depicted. As can be seen, in incorrect responses (dropped line), BPD patients showed attenuated ERN component in both central electrodes [source: (DeBruijn et al, 2006)]

Error-processing in BPD. BPD patients show an increase in the reaction time (RT) of erroneous responses compared to correct ones and attenuated ERN (de Bruijn et al., 2006; Ruchsow et al., 2006), but not Pe amplitude (Ruchsow et al., 2006). In addition, the reduced ERN amplitude has been related to self-reported impulsivity in these patients (Ruchsow et al., 2006). These two studies were performed with twelve BPD patients and twelve healthy control participants each who realized, in one case, a Go/no-Go task (Ruchsow et al., 2006) and, in the other, a Flanker task (de Bruijn et al., 2006). Importantly, Ruschsow et al (2006) refuse any correlation between ERN amplitude and medication in the BPD patients group.

These are the two only studies which have investigated the electrophysiological response associated with error detection and inhibition in BPD (see Figure 16B). Both demonstrated a reduced action monitoring in BPD patients and suggested that they do not learn from their errors (relative to controls).

5. Summary of the introduction

- BPD is a complex and serious mental disorder with a characteristic pervasive pattern of instability on affect regulation, impulse control, inter-personal relationships and self-image. Patients with this disorder usually require more mental health resources than individuals with other psychiatric disorders, generating important social costs.

- Despite their causes being unknown, a biological vulnerability which interacts with certain early adverse environmental factors has been proposed. Continuous transactions between them cause a characteristic global emotion dysregulation, which is considered the primary dysfunction in the BPD.

- Neuropsychological studies have provided inconsistent results and, therefore, the nature of the impairments encountered is under debate.

- Neuroimaging data has been inconclusive. Nevertheless, structural alterations mainly in amygdala and hippocampus are evidenced. In addition, in fMRI experiments, the most common finding has been an exaggerated activity in the amygdala along with a weakening of prefrontal inhibitory control, during procedures that involve the processing of emotional aversive stimuli.

- Non-suicidal self-injury behaviours are one of the most prominent symptoms of BPD. Numerous studies have suggested that poor cognitive control, failure in self-regulation, alterations in feedback processing (*e.g.* social) or the necessity for endogenous opiate system self-stimulation (among others), are all involved in these maladaptive behaviours.

- The reward brain circuit plays a crucial role in learning, self-regulation and in environmental adaptation. Several findings support a dysfunctional reward system in BPD.

- Preserved executive control is necessary for a proper self-regulation. Here, on one hand, metacognition skills are required for top-down regulation of information processing. On the other hand, to detecting errors appropriately is necessary for adjusting behaviuor accordingly.

6. Aims and hypotheses

The general aim of this piece of research was to study reward processing and cognitive control in BPD patients, taking into account the presence of non-suicidal self-injury behaviours. In particular, we conducted four experiments in order to evaluate the neurophysiological correlates of the reward system (Chapter II: study 1 and 2) and the involvement of cognitive control in the regulation and inhibition of behaviour (Chapter III: study 3 and 4) in these patients. Two of these experiments (study 2 and 3) also introduced non-suicidal self-injury behaviours as an independent variable.

6.1. Specific aims and hypotheses

6.1.1. Study 1 and 2: Reward system in BPD patients

The reward-brain brain network is related to a variety of motivated behaviours and cognitive processes, such as reinforcement learning, action monitoring, novelty processing learning, decision making and economic choice or incentive motivation. The aims of this section and the corresponding hypotheses are:

i. To study two reward-related ERP components, the Feedback-Related Negativity and the Theta oscillatory activity, in a sample of BPD patients. We predict that losses would have less impact in BPD patients than in healthy participants (reduced negative prediction error) yielding a reduction in the amplitude of the FRN component and theta oscillatory activity (study 1).
ii. To study the modulation of brain regions involved in reward processing, using functional neuroimaging (fMRI) in a sample of BPD patients (study 2). We

predict that the BPD group shows alterations in reward related brain regions in comparison with the control group.

iii. To determine specific alterations in the modulation of the brain regions involved in reward processing, using functional neuroimaging (fMRI), in BPD patients in function of the presence (or not) of non-suicidal self-injury behaviours. We expect that BPD patients who recurrently engage in NSSI behaviours would show brain functioning differences in reward processing when compared to those with non-NSSI behaviours and also to healthy controls. In particular we would expect alterations in the reward-related regions involved in high-order cognitive control and associative learning (i.e. OFC) (study 2).

6.1.2. Study 3 and 4: Cognitive control in BPD patients:

Cognitive control refers to those psychological and neural mechanisms by which people actively remember and maintain information such as goals, instructions, plans, or specific prior events for short periods of time, and can then use this information to appropriately guide and control their behaviour. An interesting aspect of cognitive control is metacognition, which refers to the capacity to reflect upon and evaluate cognition and behaviour. This is an important construct in order to understand how BPD patients consolidate their self-image on control and regulation capacity which, in turn, have an impact on their behaviour. The aim of this section is:

i. To evaluate the neurophysiological correlates of a core aspect of cognitive control and regulation, error processing [indexed by the Error-related Negativity (ERN), Error positivity (PE) and the Theta oscillatory component],

in BPD patients according to their tendency to commit non-suicidal behaviours (study 3). We predict that BPD patients would present reduced ERN amplitude after error commission, indicating an alteration in cognitive control mechanisms. In addition, we expect that those BPD patients with a non-suicidal self-injury history would show a larger reduction in ERN and Pe components compared to those without one, indicating a more severe impairment in the cognitive control system .

ii. To evaluate the metacognitive abilities of BPD patients in relation to the monitoring of self-regulatory and cognitive control mechanisms (study 4). We expect that BPD patients would show monitoring deficits (a low metacognitive accuracy) in their self-regulation abilities used in everyday functioning.

7. General methods and procedures

A total of sixty BPD patients and thirty-six healthy participants were enrolled in the experiments included in the present thesis. All participants were females and were aged between 18 and 45 years old.

All BPD participants were outpatients of the Psychiatry Department of the Hospital of Igualada (Barcelona, Spain). They met the diagnostic criteria according to DSM-IV-TR and underwent a double diagnostic interview by independent evaluators trained in the administration of the Spanish version of the Diagnostic Interview for Borderlines-Revised (DIB-R, see bellow), in order to ensure the diagnosis. The presence of brain injury, psychotic, bipolar, or current major depressive disorder, drug or alcohol abuse in the previous month, and Intelligence quotient (IQ) below 80 were exclusion criteria.

On the other hand, the healthy participants were recruited via local advertisement and presented no current or previous psychiatric disorder.

All experiments included in the present dissertation followed the Declaration of Helsinki and was approved by the local Scientific and Ethics Committee. In addition, the participants were paid.

Of the initial sample, fifty-one BPD patients and thirty healthy participants completed the ERP procedure (study 1 and 3). On the other hand, forty-nine BPD patients and twenty-three healthy participants completed the fMRI procedure (study 2). In the four experiments included in this thesis, different subgroups of participants were used.

Once we evaluated the first eighteen BPDs and eighteen healthy participants, the study 1 was completed (further analysis of the data has shown that the results are maintained with a larger sample).

Secondly, the study 4 was conducted with thirty-four BPD patients and seventeen healthy controls. In this experiment, the rest of ERP-records were not included for different technical reasons (*e.g.* movement).

Thirdly, forty BPD patients and twenty healthy controls were included in the study 2. In this experiment several fMRI-records were excluded for movement problems and for matching samples in age and IQ.

Finally, in the study 3 we included thirty-six BPD patients, who agreed to be evaluated by their relatives, and the thirty-six healthy controls.

Chapter II:

Study of the reward system in the BPD ♣,♦

♣Vega, D., Soto, A., Amengual, J.L., Ribas, J., Torrubia, R., Rodriguez-Fornells, A., Marco-Pallarés, J. (2013). Negative reward expectations in Borderline Personality Disorder patients: Neurophysiological evidence. *Biological Psychology, 94,* 388 - 396.

♦Vega, D., Ripollés, P., Soto, A., Ribas, J., Torrubia R., Monreal, J.A., Pomarol-Clotet, E., McKenna, P., Salvador, R., Rodriguez-Fornells A., Marco-Pallarés J. Alterations in the reward system differentiate Borderline Personality Disorder patients in function of the presence of non-suicidal self-injury behaviors (in preparation).

8. Reward system: ERP approach.

Negative Reward Expectations in Borderline Personality Disorder Patients: Neurophysiological Evidences

8.1. Introduction

Borderline Personality Disorder (BPD) is a complex and serious mental disorder with a characteristic pervasive pattern of instability on affect regulation, impulse control, interpersonal relationships and self-image, and severe functional impairment (Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004). Although it seems to be a heterogeneous and less stable diagnosis (Zanarini, Frankenburg, Reich, & Fitzmaurice, 2010), emotion dysregulation is the most permanent and frequent criterion (Carpenter & Trull, 2013; Glenn & Klonsky, 2009). Some influential accounts on the etiology of BPD propose that patients present an impairment in the processing of critical information in the adaptation of behavior to environmental contingencies (e.g., rewards and punishments associated to their actions) which would compromise their emotional self-regulation (Crowell, Beauchaine, & Linehan, 2009). Nevertheless, studies on the processing of rewarding outcomes as well the expectations of receiving a reward have been scarce in these patients.

Emotional reactivity and cognitive control have been proposed as two features of the BPD emotional difficulties and, additionally, have been related to their attachment style which plays a central role in the development of the disorder (Agrawal, Gunderson, Holmes, & Lyons-Ruth, 2004; Minzenberg, Poole, & Vinogradov, 2008; Steele & Siever, 2010). Rodent models and human neuroimaging have related the attachment system with the reward network due to a shared neural circuit which links a neuropeptide-sensitive mechanism (oxitocin/vasopressin), within the anterior hypothalamus, to the ventral tegmental area (VTA) and nucleus accumbens (see for a

review Insel & Young, 2001). In addition, from a gene-environment perspective, the dopamine DRD4 polymorphism in children has been related to disorganized attachment patterns with parents (Lakatos et al., 2000). The reward system is related to a variety of motivated behaviors and cognitive processes, such as reinforcement learning, novelty processing, action monitoring, decision making or addiction (Camara, Rodriguez-Fornells, Ye, & Münte, 2009). Therefore, the interaction between these two systems (reward and attachment) may be especially important for mediating the rewarding properties of social interaction as salient-motivating cue, and for affect and stress regulation (Strathearn & Mayes, 2010; Vrticka, Andersson, Grandjean, Sander, & Vuilleumier, 2008).

The idea of a dysfunctional reward system in the BPD has received growing theoretical interest in recent years (Bandelow, Schmahl, Falkai, & Wedekind, 2010; Friedel, 2004). Previous research has reported impaired opioid activity, linked with the reward system (Prossin, Love, Koeppe, Zubieta, & Silk, 2010). Furthermore, empirical data show that the BPD individuals make impulsive choices that result in fast appetitive rewards (Dougherty, Bjork, Huckabee, Moeller, & Swann, 1999; Lawrence, Allen, &Chanen, 2010). Several studies have been suggested a dysfunctional reinforcement processing during both rewards and loss feedbacks (Kirkpatrick et al., 2007; Völlm et al., 2007). A recent event-related brain potential (ERP) study (Schuermann, Kathmann, Stiglmayr, Renneberg, & Endrass, 2011) showed reduced amplitude on the Feedback-Related Negativity (FRN) component in BPD patients (relative to controls) who were performing an Iowa Gambling Task. Interestingly, this ERP component is elicited 250-300 ms after the presentation of a feedback, indicating a monetary loss or incorrect action (Gehring & Willoughby, 2002; Miltner, Braun, & Coles, 1997). The dynamics of the FRN have been explained using the reinforcement learning model (Holroyd &

Coles, 2002) which proposes that the FRN is indirectly reflecting the influence of decrease in VTA dopaminergic signals in the midbrain after unexpected punishments (Schultz, 1998). This reinforcing signal might be transmitted to the ventral striatum, as well as other cortical regions such as the medial prefrontal cortex. The FRN has been associated with a possible teaching signal concerning *worse than expected* consequences of actions. Considering this proposal, unexpected negative outcomes should elicit larger amplitude in the FRN component than unexpected positive outcome. In addition, several studies have described an enhancement of theta power activity after negative outcomes, which might not only be related to ACC activity, but also might reflect a broader neural network involved in the orchestrating adaptive adjustments after errors or negative feedbacks (Cohen, Elger, & Ranganath, 2007; Marco-Pallares et al., 2008). No previous research has studied theta power modulations in the BPD.

In the present study we evaluated the neurophysiological correlates (ERPs and theta oscillatory activity) associated with reward processing in a sample of BPD patients. In contrast to previous studies (Schuermann et al., 2011) we used a paradigm where the outcomes were not predictable, a monetary gambling task in which participants had to choose between two numbers in order to win or loss real money. In this paradigm the behavior is not guided by objective probabilities of receiving a reward or punishment (as for example, in reversal learning tasks or the Iowa Gambling Task; Schuermann et al., 2011), but by internal expectations as rewards and punishments are delivered at random. Therefore, we aimed to study the differences between BPD and healthy subjects associated to an uncertain environment or contexts in which clear predictions about the outcome of their actions were not possible. In addition, this paradigm has been shown to provide a very reliable FRN component and theta oscillatory activity in loss trials (Gehring & Willoughby, 2002, Marco-Pallares et al.

2008, Marco-Pallares et al. 2009). We hypothesized that the characteristics of the present gambling task, in which there is neither correct response nor objective rule, could induce a differential behavioral pattern in BPD patients compared to healthy participants, especially in their risky choice patterns (that is, the tendency to increase their risk after certain outcomes; Gehring & Willoughby, 2002; Padrao et al 2013). In addition, given the tendency of BPD to form unrealistic goals and negative expectations about the outcomes of their actions (Crowell, Beauchaine, & Linehan, 2009), we hypothesized that monetary losses would have less impact in BPD patients than in healthy participants (reduced negative prediction error), yielding a reduction in the amplitude of the FRN component and theta oscillatory activity.

All these hypotheses were tested in a group of BPD women (double diagnostic interview by independent evaluators). Complementarily to the clinical instruments, and in order to better characterize the reward system in the sample and to control the individual differences in reward processing between patients and healthy participants, we used the Sensitivity to Reward and Punishment scales (Torrubia, Ávila, Moltó, & Caseras, 2001), to measure approach-avoidance conflicts at cognitive level which could bias feedback processing (for a review on decision making and emotion regulation see Mitchell, 2011). Finally, as previous studies have shown that certain psychopharmacological drugs could affect the ERPs components as well as the responsiveness of the reward brain system (see for example: Abler, Grön, Hartmann, Metzger, & Walter, 2012; Johannes, Wieringa, Nager, Dengler, & Münte, 2001) a protocol to assess total medication load, previously used in psychiatric samples (Vederman et al., 2012), was used to control possible confounding effects.

8.2. Methods

8.2.1. Participants

Thirty-six women ranging in age from 18 to 45 years old were included in the study. The BPD participants were 18 outpatients of the Psychiatry Department of the Hospital of Igualada (Barcelona, Spain) who met the diagnostic criteria according to DSM-IV-TR (APA, 2000). The Healthy Control (HC) group consisted of 18 healthy women recruited via local advertisement without history of any psychiatric disorder. The exclusion criteria were the presence of brain injury, psychotic, bipolar, or current major depressive disorder, drug or alcohol abuse in the previous month, and an Intelligence Quotient (IQ) below 80. Groups were matched by age and IQ. The participants were paid, and the study followed the Declaration of Helsinki and was approved by the local Scientific and Ethics Committee.

The BPD patients underwent a double diagnostic interview by independent evaluators trained in the administration of the Spanish validation of the Diagnostic Interview for Borderlines-Revised (Barrachina et al., 2004), in order to ensure the diagnosis. Both BPD and HC groups were assessed with a Spanish adaptation of the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (Pérez-Prieto et al., 2008) and for DSM-IV Axis I (First & Gibbon, 1997). The BPD depressive symptoms ranged from 4 to 17 (M = 11.55, SD = 4.27) in the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). Medication prescription in the BPD group was stable along the study (M = 2.33, SD =1.84, range: 0-5). The selective serotonin reuptake inhibitors (N = 10) and benzodiazepines (N = 9) were the most used, followed by mood stabilizers (N = *7)*, atypical antipsychotics (N = 4) and another type of drugs

such noradrenergic and serotoninergic antidepressants (*N* = 5). Demographic and clinical variables can be observed in table 1.

Table 1. Demographic characteristics, clinical and psychometric variables.

	BPD (n=18)		HC (n=18)			
	Mean	SD	Mean	SD	*t*-Test	p value
Age (years)	30.94	5.96	27.44	6.9	1.62	.11
IQ	96.85	8.49	99.46	8.05	-0.94	.35
DIB-R (First)	8.06	0.93			0.54	.59
DIB-R (Second)	7.89	1.18				
SPSRQ						
SR	11.38	4.11	6.94	3.4	3.52	.001
SP	17.66	4.76	9.22	5.01	5.18	<.001
VAS						
Receive-Max	58.94	26.71	60.61	22.31	-0.20	.840
Receive-Min	23.22	23.35	28.11	25.96	-0.59	.557
Lose-Max	59.72	24.27	44.11	24.69	1.91	.064
Lose-Min	12.88	15.82	12.16	12.4	0.15	.879
	n	(%)	n	(%)	χ^2-Test	p value
Right-handed	15	83.3	17	94.4	1.12	.316
SCID-I (current)						
Anxious disorder	10	55.5				
Eating disorder	5	27.7				
Substance misuse	7	38.8				
Dysthymia	4	22.2				
SCID-I (lifetime)						
MDD	14	77.8				
Anxious disorder	4	22.2				
Eating disorder	7	38.8				
Substance misuse	6	33.4				
SCID-II						
Dependent	4	22.2				
Avoidant	3	16.6				
Paranoid	1	5.5				
Histrionic	1	5.5				
Antisocial	5	27.7				

IQ, intelligence quotient, estimated through matrix reasoning, vocabulary and digits span subtests (WAIS-III); GAF, Global Assessment of Functioning; SPSRQ, Sensitivity to Punishment and Sensitivity to Reward Questionnaire; SP, Sensitivity to Punishment; SR, Sensitivity to Reward; VAS, Visual Analog Scale; DIB-R, Diagnostic Interview for Borderlines-Revised; MDD, Major Depressive Disorder.

8.2.2. Materials

Self-report measures. The Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ, Torrubia et al., 2001) is a questionnaire elaborated and

validated directly on Gray's personality model (Corr, 2004) and consists of two scales: the Sensitivity to Punishment scale (SP), which measures individual differences on Behavioral Inhibition System functioning, and the Sensitivity to Reward scale (SR), which measures individual differences on Behavioral Activation System functioning.

To assess the assigned value given by participants to a determined amount of money, a scale was created *ad hoc*. It consisted of four visual analog scales (VAS) which ranged from 0 to 100 points. The first two aimed to assess the subjective impact produced by the possibility of receiving a certain amount of money (100 euro and .50 euro cent), and the others were used for the assessment of the subjective impact produced by the possibility of losing a given amount of money (100 euro and .50 euro cent). High scores indicated that participants evaluated the impact of a possible loss/gain as very important for themselves. This measure aimed to capture the impact of possible economic feedbacks considering four possibilities (depending on valence and magnitude) in a daily virtual scenario.

Medication Load. This scale is a protocol to assess total medication load, previously used in psychiatric samples (Vederman et al., 2012). For the implementation, anti-depressant, anxiolytic, mood stabilizer, and anti-psychotic medications were coded as absent = 0, low = 1, or high = 2, based on previously employed methods to convert each medication to a standardized dose (Almeida et al., 2009; Sakheim, 2001). Anti-psychotics were converted into chlorpromazine dose equivalents (Davis & Chen, 2004). As a result, we obtained a composite measure of total medication load by summing all individual medication codes for each individual medication within categories for each BPD patient.

Gambling Task. A monetary gambling task similar to the one described by Gehring & Willoughby (2002) was used (see Figure 1A). In this task two numbers (25 and 5) were presented on a computer screen. Participants had to make an obligatory left or right mouse button press response with their right index-finger, indicating the number they wanted to bet. For instance in case of a [25][5] display, a left button press indicated the selection of the number 25, and a right button press the selection of the number 5. After the selection, one of the numbers turned red while the other turned green. If the number selected changed to red, the participant lost the corresponding amount in Euro cents, whereas if subject selected the green number he won this amount in Euro cents. After two seconds, the following trial began with the presentation of a warning signal ("*"; 500 ms duration), followed by a new set of numbers. Participants began the task with an initial 1,000 points (1 point = 1 Euro cent) and were encouraged to gain as much as possible and were familiarized with the task during a brief practice block.

The experiment comprised 17 blocks with 40 trials each, with the mean expected value of monetary outcome of zero on each block, to avoid potential confounding influences of a differential probability of gains or losses. Every 10 trials, the accumulated amount of money was presented for 7 seconds, and at the end of the experiment, the participants were paid the final amount.

8.2.3. Procedure

The clinical interviews (DIB-R only BPD group) and self-reported, intelligence and socio-demographical were gathered by a trained clinicians.

EEG (Synamps, Neuroscan) was recorded at 250 Hz sampling rate (0.01 Hz high pass filter, 50 Hz notch filter) using tin electrodes mounted in an elastic cap and located at 29 standard positions (Fp1/2, Fz, F7/8, F3/4, Fc1/2 Fc5/6, Cz, C3/4, T7/8, Cp1/2,

Cp5/6, Pz, P3/4, P7/P8, Po1/2, O1/2) while participants were performing the gambling task. Biosignals were referenced off-line to the mean of the activity at the two mastoid processes. Vertical eye movements were monitored with an electrode at the infraorbital ridge of the right eye. Electrode impedances were kept below 5 kΩ during all the register.

8.2.4. Data analysis

Firstly, descriptive data analyses were carried out. Differences between groups concerning baseline demographic, diagnostic characteristics, and self-report data, were tested using Pearson's Chi-square test (χ^2) for the categorical variables and two-tailed independent Student's *t*-test to compare means. Bivariate correlations were used to measure the association between continuous variables.

Differences in risky pattern behavior between groups in the gambling task were analyzed using repeated-measures analyses of variance (ANOVA) with two within-subjects factors (Feedback valence in the previous trial [gain, loss] and Feedback magnitude in the previous trial [large, small]) and one between subject factor (group, BPD vs. HC). Reaction times were analyzed using an ANOVA analysis with one within subject-factor (Bet magnitude [25/5]) and one between subjects factor (group, BPD vs. HC).

EEG was lowpass filtered off-line to 40 Hz and feedback-locked ERPs were averaged from 100 ms prior to the feedback (baseline) to 1000 ms after it. Epochs exceeding ±100 μV in EOG or EEG were removed from further analysis. To study the time-frequency behavior of the electrical activity elicited by the feedback, four-second epochs were generated (2000 ms before and after the feedback stimulus). Epochs exceeding ±100 μV in EOG or EEG were removed from further analysis. Single-trial

data was convoluted using a 7 cycles complex Morlet wavelet. Changes in the time varying energy (square of the convolution between wavelet and signal) in the studied frequencies (from 1Hz to 40Hz; linear increase) with respect to baseline were computed for each trial and averaged for each subject before performing a grand average. For the FRN, repeated-measures ANOVA with Valence (gain, loss), Magnitude (large, small) and electrode location (Fz, Cz, Pz) as within subject factors and group (BPD, HC) as between subject factor was performed introducing the mean amplitude at the 260-300 ms time-window after feedback presentation (Marco-Pallarés et al., 2008). For wavelet analysis, we used a time-frequency range based in the maximum differences between gains and losses (200-300 ms and 300-450 ms after feedback presentation). The Greenhouse-Geisser epsilon correction was used when appropriate.

8.3. Results

Psychometric scales. The results of the psychometric scales are shown in table 1. As it can be shown no significant differences were found on the VAS scales, indicating no between group differences in the assigned value to a determined amount of money. Furthermore, the Sensitivity to Reward and the Sensitivity to Punishment were significantly higher in the BPD group than in the control group.

Behavioral Results. Participants tended to bet 25 more than 5, both in the control (56.4 $\pm$ 10.0 %) and in the BPD (56.0 $\pm$ 9.4 %) group. There were no significant differences among groups in percent of 25 choices ($t(34) = .1$, $p = 0.5$). However, when analyzing the pattern of risky choices considering previous outcome (based on Gehring & Willoughby, 2002), a differential behavior pattern among groups was observed (Figure 1B). Repeated-measures ANOVA with two within factors (valence and magnitude) and one between-subjects factor (group) revealed a significant main effect

for magnitude ($F(1,34) = 4.4$, $p = 0.04$), which was significantly different in the two groups (magnitude x group, $F(1,34) = 5.6$, $p = 0.02$). Therefore, as shown in Figure 1B, this interaction indicated that control participants increased their risk (betting more on 25 than 5) after winning or losing the largest amount of money (25; magnitude effect for control participants, $F(1,17) = 6.5$, $p = 0.02$). In contrast, BPD patients did not show this adjustment pattern, and bet independently from the outcome of the previous trial (magnitude effect, $F(1,17) = .08$, $p = 0.8$, see Figure 1B).

In addition we also found a marginal significant valence x magnitude effect ($F(1,34) = 3.5$, $p = 0.07$) but without a group effect (valence x magnitude x group $F(1,34) = 0.564$, $p = 0.5$). Neither valence ($F(1,34) = 1.3$, $p = 0.3$) nor the interaction between valence and group ($F(1,34) = 1.5$, $p = 0.2$) yielded further significant effects. Thus, regarding trial-by-trial risk-sequential adjustments, the choices of the BPD group were uninfluenced by the outcome received in the previous trial, a pattern that is clearly different from the one observed in the control group and from the results obtained in previous investigations (Camara et al., 2010; Gehring & Willoughby, 2002; Masaki, Takeuchi, Gehring, Takasawa, & Yamazaki, 2006; Padrao et al., 2013).

Additionally, a reaction time analysis was conducted. The ANOVA revealed a marginal main effect of the bet magnitude ($F(1,34) = 3.9$, $p = .06$) indicating a fast betting to 25 than 5. No significant bet magnitude x group interaction was found (BPD: bet 25, $M = 696$ ms, $SD = 236$; bet 5, $M = 725$ ms, $SD = 280$; HC: bet 25, $M = 652$ ms, $SD = 324$; bet 5, $M = 687$ ms, $SD = 338$; $F(1,34) = .04$, $p = 0.8$).

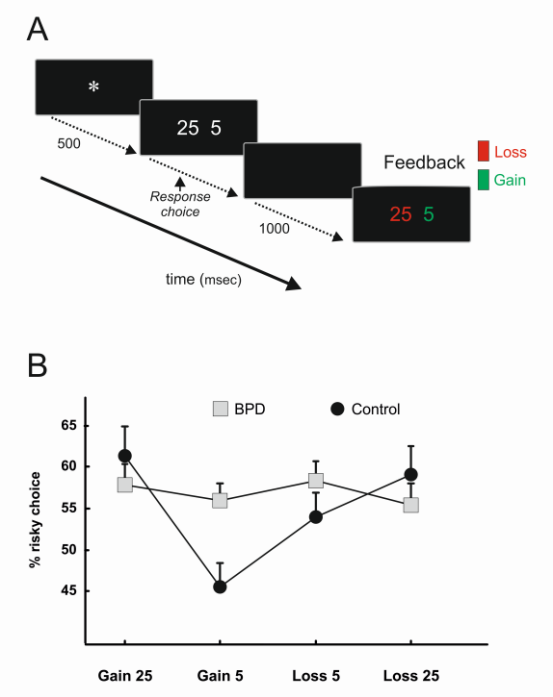


Figure 1. A. Gambling paradigm used in the experiment. B. Effect of previous trial (n-1, *x* axis) in the risk pattern observed in the following trial (percent of choice of 25 instead of 5), in the BPD and control groups. The lines represent the percent of behavioral risky choices (total bets to 25) in function of the feedback received in the previous trial (four possible outcomes: *gain 25, gain 5, loss 5 and loss 25)*. Notice the lack of sequential adjustment of risk patterns in the BPD patients when compared to the control group.

ERP data. Figure 2A shows the Event Related Potentials associated with the four different feedback conditions (gain 25, gain 5, loss 25, loss 5). In the 260-300 ms time range the negative feedbacks (monetary losses) presented a negative deflection compared to monetary gains compatible with the FRN ERP (Gehring & Willoughby, 2002; Marco-Pallares et al., 2008). A repeated measures ANOVA carried out at this time range with feedback valence (gain/loss), feedback magnitude (25/5) and electrode location (Fz, Cz, Pz) as within-subject factors and Group (BPD/Control) as between-subject factor revealed a main significant effect of valence ($F(1,34) = 40.1$, $p < 0.001$), indicating the increase of negativity observed after negative feedbacks. This effect presented a standard frontocentral topography (see Figure 2B) as revealed by a significant valence x electrode interaction ($F(2,68) = 16.0$, $p < 0.001$). Analysis also revealed a significant magnitude effect ($F(1,34) = 7.3$, $p = 0.01$), indicating an increase in activity for large as compared to small feedbacks (25 > 5).

Figure 2B shows the different waveforms (monetary loss minus monetary gains) for the Fz and Pz electrodes. The control group presented a larger FRN than the BPD (significant valence x group interaction, $F(1,34) = 4.5$, $p = 0.04$). Post-hoc analyses revealed no significant differences between groups in the gain ($t(34) = 1.0$, $p = 0.3$), nor in loss conditions ($t(34) = -0.07$, $p = 0.9$), but in the loss minus gain condition ($t(34) = -2.13$, $p = 0.04$). Interestingly, previous studies have suggested that the difference waveform is the best marker of the FRN processing (Holroyd 2004). Finally, in order to discard any effect associated to the medication, we analyzed the medication load, including it as a covariate in the repeated-measures ANOVA in the BPD group. There was no significant valence x load interaction ($F(1,16) = 1.2$, $p = 0.3$).

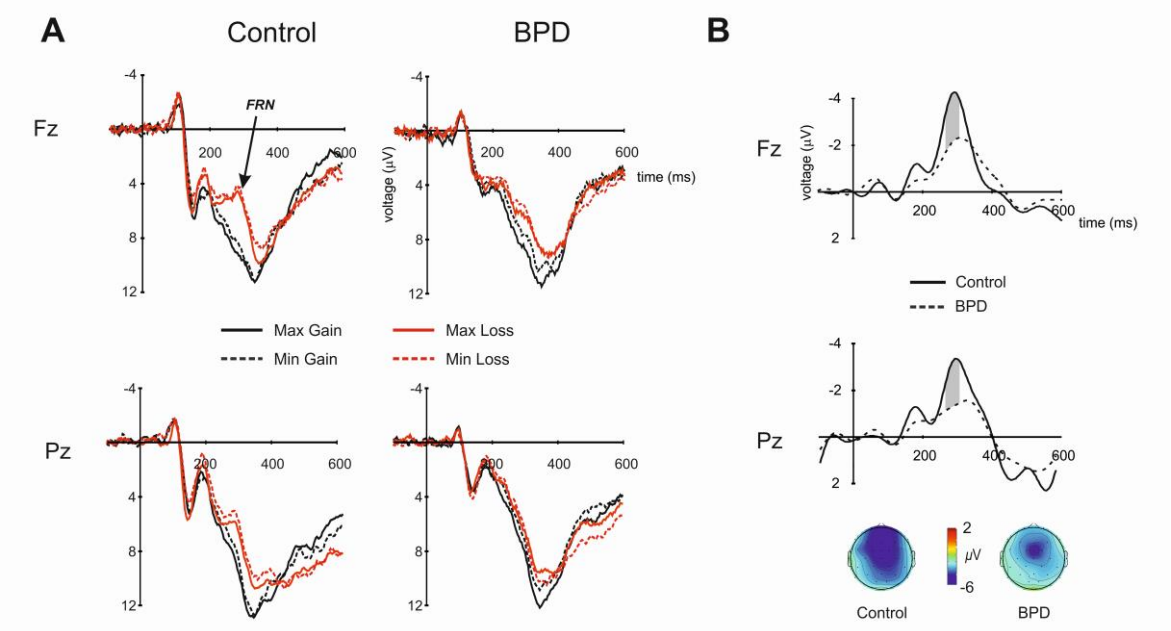


Figure 2. A. ERP associated to the four studied types of feedback: maximum gain (solid black), minimum gain (dashed black), maximum loss (solid red) and minimum loss (dashed red) for the control (left) and BPD group (right) at three midline electrode locations (Fz, Cz, Pz). Notice the increase of negativity between 260 and 300 ms for negative feedbacks compared to positive ones in the control group (FRN). This effect is reduced in the BPD group. B. Loss minus gain difference waveform at the Cz electrode for the control (blue) and BPD (orange) group. For illustration purposes, activity has been filtered with a 12 Hz lowpass filter. Region in green indicates significant differences between groups (260-300 ms). Bottom, scalp topographical maps for the

difference waveform (loss minus gain) in the green region for controls (left) and BPD (right).

Time-frequency. Figure 3 shows the power changes at frequencies between 1 to 40 Hz associated with positive and negative feedbacks for the control (Figure 3A) and the BPD (Figure 3B) group at the Fz electrode. Monetary losses were characterized by greater theta band activity (3-7 Hz) for negative feedback compared to positive feedback. We analyzed two different time ranges at this frequency band: 200-300 ms and 300-450 ms after feedback presentation. In the former time range, we found a significant valence x electrode interaction ($F(2,68) = 19.7$, $p < 0.001$), showing an increase in theta band for loses compared to gains at frontocentral electrodes (Figure 3A and 3B), but not a main valence effect ($F(1,34) = 0.1$, $p = 0.7$). There was no significant effect of group in the valence (valence x group, $F(1,34) = 2.4$, $p = 0.13$; valence x electrode x group, $F(2,68) = 2.1$, $p = 0.14$). We also found a significant magnitude effect in this time range ($F(2,68) = 8.2$, $p < 0.01$) but not a significant interaction between magnitude and electrode ($F(2,68) = 1.9$, $p = 0.2$). None of this interactions yielded a significant group effect (magnitude x group, $F(1,34) = 1.1$, $p = 0.3$; magnitude x electrode x group, $F(2,68) = 0.3$, $p = 0.8$). All the other effects were not significant ($F < 1.6$, $p > 0.2$).

Then we analyzed the 300-450 ms time range. Again, frontocentral electrodes showed a greater theta power for losses than gains (valence x electrode, $F(2,33) = 18.8$, $p < 0.001$), and the corresponding ANOVA revealed significant differences between control and BPD groups in the 3-7 Hz and 300-450 ms time-frequency range (valence x group, $F(1,34) = 4.8$, $p = 0.04$), indicating that the difference between gains and losses in the control group was higher than in the BPD group. Post-hoc analyses again revealed no significant differences between groups in the gain ($t(34) = -1.3$, $p = 0.2$), nor in loss conditions ($t(34) = -0.07$, $p = 0.9$), but in the loss minus gain condition ($t(34)$

= 2.2, p = 0.04). However, we found a marginal significant interaction of valence and medication load for valence in the BPD group (valence x load $F(1,16) = 3.1$, $p = 0.099$). In order to determine the origin of this marginal effect, we divided the medication load between different groups: antidepressants, anxiolytics, antipsychotics and anticonvulsants. We did not found significant differences with any of the specific medication types (antidepressants, $F(1,16) = 0.9$, $p = 0.4$; antipsychotics, $F(1,16) = 1.3$, $p = 0.3$; anxiolytics, $F(1,16) = 1.1$, $p = 0.3$; anticonvulsants $F(1,16) = 2.6$, $p = 0.13$).

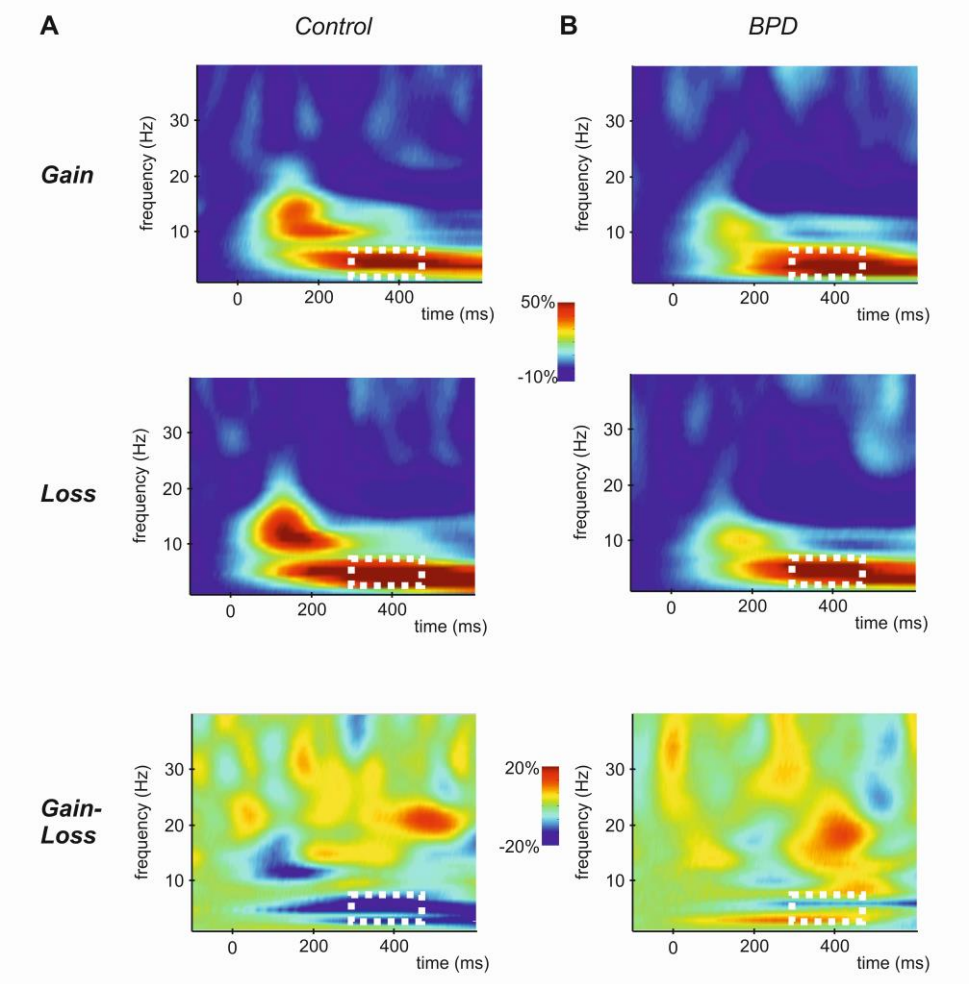


Figure 3. Time-frequency plots at the Fz electrode for (A) the control and (B) the BPD group. From top to bottom can seen the power changes at the frequencies between 1 and 40 Hz of: gain, loss and gain minus loss. The white rectangle indicates the time-frequency studied area for the theta band (3-7 Hz, 300-450 ms).

8.4. Discussion

Reward-related feedback processing in a group of BPD patients was evaluated, analyzing behavioral adjustments (change on risky patterns), the feedback related negativity ERP component (FRN) and the time frequency decomposition of EEG after receiving monetary gains and losses (theta band power). A decrease in the amplitude of the FRN component and of the power of theta activity for the BPD group in comparison to the control group was encountered, suggesting an altered pattern of negative feedback processing which could indicate an impairment in the reward system of BPD patients. This deficit might not only be related to the valence, but also to unexpectedness of the outcome which might lead the patients to an incapacity for adjusting their behaviors and making predictions according to the history of previous outcomes.

These results are only partially in line with previous research findings (Kirkpatrick et al., 2007; Völlm et al., 2007) which have suggested an altered reward processing in the BPD patients, following both positive and negative feedback (compared with controls). Interestingly, a recent study by Schuermann et al. (2011) using an Iowa Gambling Task has shown that BPD patients made more risky choices than healthy participants and did not improve their performance nor learn during the task. Therefore BPD patients showed a reduced ability to learn from feedback. In addition, BPD patients also showed reduced FRN amplitude following both positive and negative feedbacks. Our results also suggest that BPD patients present an impairment in behavioral pattern indicated by the lack of adjustment after large magnitude gains and losses, but without an increasing in the percentage of high magnitude bets. In addition, our study showed a reduction in the FRN amplitude (Schuermann et al. 2011) and theta oscillatory activity (the latter, however, correlating with medication load).

The FRN and theta activity reduction found in the BPD group could indicate a reduction in the prediction error after the negative feedback, which could be yielded by a reduced impact of the losses in BPD patients and/or a greater expectancy of receiving punishments (Hajcak, Moser, Holroyd, & Simons, 2007). These results are of great importance because a correct processing of the environment contingencies (rewards and punishments) is required for the formation of suitable predictions and expectations, which will optimize the behavioral adaptation. In this context, the FRN component indexes the motivational impact of the outcome event more than the information content of the negative feedback (Gehring & Willoughby, 2002). More specifically, Holroyd and Coles (Holroyd & Coles, 2002) proposed that both the FRN as well as the theta activity increase appears after worse than expected results of our actions, which might be related to a brain signature conveying information of a prediction error, that is, the discrepancy between the real and the expected outcome of our actions (Cavanagh, Cohen, & Allen, 2009; Chase, Swainson, Durham, Benham, & Cools, 2011; Talmi, Fuentemilla, Litvak, Duzel, & Dolan, 2012). Therefore, when negative feedback is unexpected or the loss is greater than predicted, the FRN and theta activity would be higher, as is the difference between real and expected outcome. However, it is important to note that recently a new interpretation of the FRN has been proposed (Holroyd, Pakzad-Vaezi & Krigolson, 2008). According to this account, negative feedbacks would produce a standard N200 (the FRN) and, in contrast, positive feedbacks would elicit a positive-going deflection which would superpose to the N200-FRN, reducing its amplitude. Therefore, the important effect would be the reduction of FRN with positive outcomes, constituting the so-called feedback correct-related positivity (fCRP). Following a similar rationale, Hajihosseini & Holroyd (2013) proposed that the activity in the ACC after unexpected positive outcomes would reduce both the theta oscillatory

activity and the N200 Event-Related Potential in gain trials. According to this interpretation, the reduction in the FRN found in BPD patients could be explained by a reduction in the N200 amplitude due to a decreased novelty processing associated to both gain and loss events (see, e.g., Folstein & Van Petten, 2008, for a N200 review). In other words, this account would suggest that BPD patients would be less sensible to the novel impact associated to the feedback processing. However, there is still an open debate on the interpretation of the FRN-fCRP ERP components and more studies are needed in order to establish a correct functional interpretation for these responses.

The BPD group scored high both in SR and SP. Thus, while the high SR scores could indicate a pervasive tendency to pursue fast appetitive rewards, at the same time, the high scores on SP could suggest an underestimation of potential rewards and overestimation of possible risks, punishment or non-rewarding outcomes (Corr, 2002). This combination, in addition with alterations in the feedback processing (FRN), could lead them to constant conflicts at the cognitive level and emotional instability which was indirectly showed by the SPSRQ (Amodio, Master, Yee, & Taylor, 2008). To complement the SPSRQ, we created *ad hoc* a VAS. These scales did not show between groups differences, supporting a similar importance given to the possibility of receiving/losing a particular amount of money. This result combined by the scores of SPSRQ suggests that the reduction of FRN and theta activity is not related to a reduction of the impact of losses (as BPD patients show increased SP values) but more likely linked to an increase in the expectancy to lose.

The present results might reflect impairment in the mesolimbic dopaminergic system (Marco-Pallarés et al., 2009), in line with neuroimaging findings (see for a review Mauchnik & Schmahl, 2010). In addition, some theoretical approaches to

borderline etiology (Bandelow et al., 2010; Friedel, 2004) as well as some clinical traits such as emotion dysregulation or impulsivity, psychotic-like symptoms and partial efficacy of antipsychotic drugs among others, also suggest a deregulation of the reward system in these patients. Furthermore, the current results are in line with previous research showing that the Error Related Negativity, a parallel component which appears after the commission of an error (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993) is also reduced in BPD patients, suggesting an impaired capacity to learn from errors and to implement sequential cognitive control adjustments (de Bruijn et al., 2006; Ruchsow et al., 2006). It is important to note that, according to the reinforcement learning theory (Holroyd & Coles, 2002), the FRN acts as a teaching signal after worse than expected events (negative prediction error, but see Holroyd et al., 2008) and it might be used to reinforce correct responses and inhibit erroneous ones. Impairment on this signal might result in non-optimal adaptation of behavior after errors or negative feedbacks. While in the present experiment there is no correct strategy *per se* (as rewards and punishments were delivered at random without participants' knowledge), differences in the behavioral adjustments (risk patterns) between control and BPD group supports this idea (see Figure 1B). The risk pattern in the control group is very similar to the one found in Padrao et al, 2013 (but see Gehring & Willoughby, 2002). In the two studies, control participants showed an increase in their risky decisions characterized by a greater selection of high magnitude choice after large magnitude outcomes (whether monetary gains or losses). Interestingly, this patter differs from the one shown in Gehring & Willoughby (2002), in which the risky-choice pattern increased linearly, from high gains to high losses. However, it is important to note that both experimental paradigms are slightly different, being the current paradigm a simplified version of the Gehring &

Willoughby (2002) (see Marco-Pallares et al, 2008). In contrast, BPD patients showed a flat risky-choice pattern, with similar percentage of high magnitude selection after any outcome. This behavior seems to suggest that patients did not use previous information and bet independently from the outcome of the previous trials. This result is also similar to the reduced risky choices after large magnitude trials in participants with high values in the anhedonia trait (Padrao et al., 2013). In addition, patients with high pathological anxiety also show a reduced tendency to risk, especially after small gains (Giorgetta, et al. 2012). Other studies have shown that schizophrenic patients reduce the exploration of uncertain scenarios with higher risk (Strauss et al., 2011). It has also been proposed that the decrease of risk-taking behavior might be related to reduced expectations of reward in the future (pessimistic evaluation of future, Giorgetta et al., 2012). However, the present results do not show a global reduction in the risk-taking behavior (the percentage of choosing 25 is the same in the two groups), but in the pattern of risky choice after different outcomes. Therefore, the lack of a sequential adjustment strategy in these patients could be explained by a reduced impact of previous trial feedback and a subsequent impairment in the activation of automatic adjustment mechanisms elicited most probably in the medial prefrontal cortex (Cavanagh et al., 2009; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Schuermann et al., 2011).

The alteration on reward processing and adjusting behavior found in present results might help understand the tendency of BPD patients to make suboptimal, even disadvantageous, decisions. Moreover, the results are in accordance with some theories about the development of BPD psychopathology, which propose that early environmental factors (i.e. invalidating developmental context or neglect) (Linehan, 1993), as well as genetic factors, could alter the reward pathways in the brainand cause "hyper-reactivity" of the attachment system (Fonagy & Bateman, 2006). This

phenomenon is a *vicious circle* between attachment style and environmental experiences, resulting in certain cognitive biases which complicate the decision making based on previous experiences and feedback, in line with current cognitive therapy proposals (Clark & Beck, 2010). Interestingly, our experimental context could be considered as an experimental model of an invalidating setting similar to that proposed by Linehan in her biosocial theory of BPD (see for a review Crowell, Beauchaine, & Linehan, 2009), in which an inconsistent use of punishment and reward by progenitors was postulated. In contrast to other experimental approaches in which risk conditions or specific rule probabilities were used (Schuermann et al., 2011), in the present study participants neither knew the probability of each choice nor whether a correct strategy existed or not. Therefore, the uncertainty created by the gambling task (winning or losing 5 or 25 at random while participants are trying to "maximize" their gains) might generate an ambiguous situation after the participants' choice, as they did not have any evidence or signal to trust in their election or strategy, which in patients might impair the capacity to use the history of previous outcomes to adjust the behavior.

The main limitation of present study arises from the fact that the BPD patients were on medication during the study which could affect the effects in brain electrical activity. However, it is important to note that the prescription was stable along the assessment process, and that the symptoms of unmedicated BPD patients could hinder (even make impossible) the experiment performance. Despite this, we have included a standardized measure given that previous findings have suggested an effect of several psychopharmacological drugs on for example, action monitoring (Riba, Rodriguez-Fornells, Munte, & Barbanoj, 2005) or reward processing (Abler, Grön, Hartmann, Metzger, & Walter, 2012). Thus, we found only a marginal effect of medication load in theta oscillatory activity, but importantly, FRN was not affected by medication. This

dissociation between the differential effect of medication in theta (marginal) and FRN (no effect) might be explained by the poorer temporal resolution of theta time-frequency analysis, which might include not just FRN, but also other components such as P300. In addition it is not possible to compare this effect with previous study on BPD and FRN/ERN (de Bruijn et al., 2007, Schuermann et al., 2011) because they did not study oscillatory activity. Nevertheless, in the present study differences in FRN between controls and BDP are not affected by medication evidencing a dysfunctional reward processing in BPD patients, concretely in the negative feedback processing which might lead to deficits in learning and decision making due to an impaired capacity to elicit correct expectations and predictions. These results contribute to understanding the BPD psychopathology supporting the emotional instability as one of the core features of the disorder. Furthermore in a clinical settings, where a common cost-benefits analysis are asked to patients, our results could contribute to a better approach to several important aspects such as the build of therapeutic alliance process (e.g. integrating it in the validation work), drug compliance and self-regulation training.

8.5. References

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9. Reward system and NSSI: fMRI approach.

Alterations in the reward system differentiate Borderline Personality Disorder patients in function of the presence of non-suicidal self-injury behaviors

9.1. Introduction

Borderline Personality Disorder (BPD) is a serious and disabling mental condition. Although BPD falls into a heterogeneous diagnostic category, the most prominent clinical characteristic of these patients is a strong alteration on affect regulation (Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004). Interestingly, during intense negative affect states, borderline patients most often incur non-suicidal self-injury behaviors (NSSI; *e.g.,* cut oneself) (Weinberg & Klonsky, 2012) which, in turn, are a public health concern (Nock, 2010).

Importantly, a recent study has shown a relationship between emotional dysregulation and reward system alterations in BPD patients (Enzi et al., 2013). This finding suggests a crucial role of the reward system in the BPD phenomenology, and fits well with previous studies on this topic (Vega et al., 2013; Völlm et al., 2007). Briefly, the reward-brain brain network is related to a variety of motivated behaviors and cognitive processes, such as reinforcement learning, action monitoring, novelty processing learning, decision making and economic choice or incentive motivation (Camara, Rodriguez-fornells, Ye, & Münte, 2009). In addition, it is also involved in the human attachment system (Insel & Young, 2001).

Notably, NSSI are a behavioral phenotype of affect dysregulation in BPD (Niedtfeld et al., 2010), which also play a role in reducing emotional distress (Weinberg & Klonsky, 2012). For instance, a thermal pain stimuli (similar to NSSI) is able to alter emotion regulation processes in BPD patients (Niedtfeld et al., 2012), eliciting an

enhanced negative coupling (inhibitory) between limbic (and para-limbic) and Prefrontal cortex (PFC) regions. Despite these evidences, no previous studies have directly tested the relationship between NSSI and the reward system in BPD patients. Curiously, the lack of research on this topic contrasts with findings in favor of a role of the Endogenous Opioid System (EOS; which is closely related with the reward system (Ribeiro, Kennedy, Smith, Stohler, & Zubieta, 2005; Roth-Deri, Green-Sadan, & Yadid, 2008)) in the affect regulation effect of NSSI (i.e., by decreasing negative affect or increasing positive affect states) (Bandelow, Schmahl, Falkai, & Wedekind, 2010; Bresin & Gordon, 2013; Stanley et al., 2010).

Bias in the processing of complex information, such as interpersonal signals (*e.g.*, fear of abandonment), is a frequent trigger for NSSI behaviors in BPD patients (King-Casas et al., 2008; Klonsky, 2007). Importantly, NSSI are not a merely impulsive acts but planned actions (Klonsky, 2007). Thus, in daily life, it seems plausible that the higher-order cognitive control abilities (*e.g.*, metacognition, planning) play an important role to successfully cope with NSSI thoughts and in the choice of alternative self-regulation strategies. In this line, one of the crucial reward-related areas involved in abstract representations is the Orbitofronal Cortex (OFC), specially its more anterior regions [frontopolar cortex: (Sescousse, Redouté, & Dreher, 2010a)]. Notably, anterior OFC regions have been associated with the processing of abstract rewards, such as money or social judgments (Sescousse et al., 2010a). Therefore, the OFC plays an important role in processing learned associations, in contrast with other sub-cortical regions mainly involved in the processing of primary rewards (such as sex), which have an innate value (Sescousse, Caldú, Segura, & Dreher, 2013).

The present study aimed to investigate the reward brain system using functional neuroimaging (fMRI) in a large sample of BPD patients. We established two matched

BPD groups, only differentiated by their engagement in NSSI behaviors, and a control group of healthy individuals. Considering the previous study of Enzi et al. (Enzi et al., 2013), which suggested that the reward system in BPD patients is not altered per se but is disturbed by altered processing of affective states, here we tested the role of NSSI in the modulation of reward-related activations using a simple gambling monetary task, free of emotional content. We hypothesized that those BPD patients who recurrently engage in NSSI behaviors would show brain functional differences in reward processing when compared to those with non NSSI behaviors and also to healthy controls. Concretely we expected alterations in the reward-related regions involved in high-order cognitive control and associative learning (i.e. OFC).

9.2. Methods

9.2.1. Participants

Participants were 60 women aged between 18 and 45 years, divided in three groups. BPD patients (N=40) were recruited in the Mental Health Area of the Hospital of Igualada (Spain) in function of: a) DSM-IV defined diagnosis of BPD and, b) presence or not of NSSI behaviors. Patients with a NSSI history comprised the SI-BPD group (N=20) and were characterized by: a) lifetime history of five or more episodes of any NSSI behavior (determined by the Inventory of Statements About Self-injury, ISAS, see below) b) two of the aforementioned episodes having occurred in the last two years (determined by the self-harm item of the DIB-R). Despite this study was developed before the presentation of the DSM-5, these criteria are compatible with the nonsuicidal self-injury disorder. In contrast, patients without NSSI behaviors constituted the NI-BPD group (N=20) and had no prior history of any NSSI behavior at the time of

study enrollment (assessed by the ISAS and DIB-R). Healthy controls (N=20) were recruited by means of local advertising, and had no previous history or current mental disorder. These three groups were matched in sex (all women), age and IQ (see Table 1). Presence of brain injury, psychotic, bipolar, current major depressive disorder, alcohol/drug dependence or an IQ below 80 was exclusion criteria. Written informed consent was obtained from all participants and all procedures were approved by the local ethical committee.

All three groups were assessed with the Spanish adaptation of the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (Pérez-Prieto et al., 2008) and with DSM-IV Axis I interview(First & Gibbon, 1997). In addition, patients were assessed with the Diagnostic Interview for Borderlines-Revised (DIB-R) (Barrachina et al., 2004) by two independent clinicians (first: 7.65 $\pm$ 1.67; second: 7.61 $\pm$ 1.25; r = 0.46, p< .01.). Comorbidity with other mental disorders is reported in Supplementary Table 1. In addition, thirty BPD patients were taking psychiatric medication at the time of scanning (SI-BPD=17; NI-BPD=13; χ^2 = 2.13, *P*=.144). Of these patients nineteen (47.5%) were taking antidepressants, six (15%) antipsychotics, nineteen (47.5%) mood stabilizers and eighteen (45%) benzodiazepines (mean average of total drugs= 1.9 $\pm$ 1.49).

Medication. The polypharmacy is common in the BPD patients' treatment. To control a possible effect of this variable on the present experiment, a well defined protocol previously used in psychiatric populations was used (Vederman et al., 2012). Accordingly, based on proposed drug-dose equivalences (Almeida et al., 2009; Davis & Chen, 2004; Sackeim, 2001), anti-depressant, anxiolytic, mood stabilizer, and anti-psychotic medications were coded as absent = 0, low = 1, or high = 2 in order to obtain

a standardized dose of each meditation. As a result, a composite measure of total medication load was obtained (see Table 1).

9.2.2. Materials

Questionnaires and tests. For BPD groups, clinical severity was assessed by means of the Borderline Symptom List [BSL-23; Soler et al., 2013], which is a self-reported measure that evaluates the BPD severity during the last week; by the Clinical Global Impression for the BPD scale [CGI-BPD; Perez et al., 2007], which was implemented by the clinician; and by the Beck Depression Inventory-II [BDI-II; Sanz, García-vera, Espinosa, Fortún, & Vázquez, 2005]. In addition, personality traits were measured using the Barratt Impulsiveness Scale [BIS-11; Patton, Stanford, & Barratt, 1995], the Agression Questionnaire [AQ; Buss & Perry, 1992] and, the Sensitivity to Reward and Sensitivity to Punnishment Questionnaire [SCSRQ; Torrubia, Avila, Caseras, & Molto, 2001].

On the other hand, a Spanish translated-version of the Inventory of Statements About Self-injury [ISAS; Klonsky & Glenn, 2008], was used to quantify lifetime frequency of 12 NSSI behaviors (*e.g.* cutting, burning, carving) and their descriptive and contextual factors (*e.g.* age of onset). For details on NSSI behaviors see Supplementary Table 2.

Table 1. Demographic and clinical summary

	SI-BPD (N=20)		NI-BPD (N=20)		Healthy Controls (N=20)		Group Differences		
	Mean	S.D.	Mean	S.D.	Mean	S.D.	F	*P*	*Post hoc*
Demographic									
Age at fMRI (years)	29.55	5,85	31.20	6.72	28.2	5.6	1.22	.30	
IQ	95.76	7.83	99.30	12.01	98.86	10.17	.72	.49	
Onset (age)[a]	24.9	5.44	26.44	5.93			-.83	.41	
Clinical									
GAF	46.4	5.4	56.57	7.52			4.87	.000	SI-BPD<NI-BPD
DIB-R	8.05	1.09	7.3	1.08			2.17	.03	SI-BPD>NI-BPD
BDI	28.55	12.64	25.15	14.61			.79	.44	
BSL-23	2.11	.98	2.06	.95			.13	.89	
CGI-BPD	5.85	.99	4.21	1.13			4.82	.000	SI-BPD>NI-BPD
Medication Load	2.5	1.73	1.8	1.64			1.31	.19	
Pesonality/Temperament									
SP	18.57	4.25	16.88	5.43	10.45	4.85	13.47	.000	BPD>HC
SR	11.76	3.79	12.78	5.71	6.45	2.78	11.49	.000	BPD>HC
BIS-11	75.44	17.31	69.51	14.81	42.55	12.87	25.55	.000	BPD>HC
AQ	110.44	20.89	100.42	20.75	50.85	11.46	60.48	.000	BPD>HC
NSSI									
Number of episodes	711.11	1188.98							

Notes. *GAF*, Global Assessment of Functioning (DSM-IV); *DIB-R*, Diagnostic Interview for Borderlines-Revised; *BDI*, Beck Depression Inventory-II; *CGI-BPD*, Clinical Global Impression for the BPD; *BSL-23*, Borderline Symptom List 23; *SP*, Sensitivity to Punishment; *SR*, Sensitivity to Reward; *BIS-11*, Barratt Impulsiveness Scale-11; AQ, Aggression Questionnaire

[a] Age at onset of any regular BPD treatment; [b] SI-BPD=NI-NSSI, BPD > Control.

fMRI Task. Two runs of an event-related monetary gambling task [see for similar tasks: (Camara, Rodriguez-Fornells, & Münte, 2010; Gehring & Willoughby, 2002)] was used (see Figure 1). Each trial started with the presentation, in the middle of the screen, of two numbers ([25 5] or [5 25]) for 2 seconds. Participants were instructed to select one of the two numbers by pressing the spatial corresponding left or right button with their right index-finger. After this, one of the numbers turned red and the other green. A green number indicated a gain of the total amount gambled (in Euro cents), while a red number indicated a loss.

Thirty standard gain and thirty standard loss trials were presented per run. The inter-trial time varied between 0 and 2 seconds. Interestingly, some studies have shown that the inclusion of boost trials enhance the fMRI response to gains and losses (Camara, Rodriguez-Fornells, & Münte, 2008). Thus, in addition to these standard feedbacks, 33% of the trials in the task included the presence of unexpected boost gains and losses, in which instead of earning or losing 5 or 25 cents, participants gained or lost 125 cents (see Figure 1). Fifteen boost gain and fifteen boost loss trials were presented per run. Additionally, 25 trials of a 3 second-long fixation cross were also presented. Unknown to the participants, the characteristics of the trial and its result (gain or loss) were decided by the computer program before the start of the experiment. Therefore, participants could not effectively learn or predict any particular pattern to gain larger amounts of money.

Every 10 trials, the accumulated amount of money was presented for 7 seconds, and at the end of the experiment, participants were paid the final amount. Before entering the scanner, all participants completed a training block to familiarize them with the task and were encouraged to gain as much money as possible.

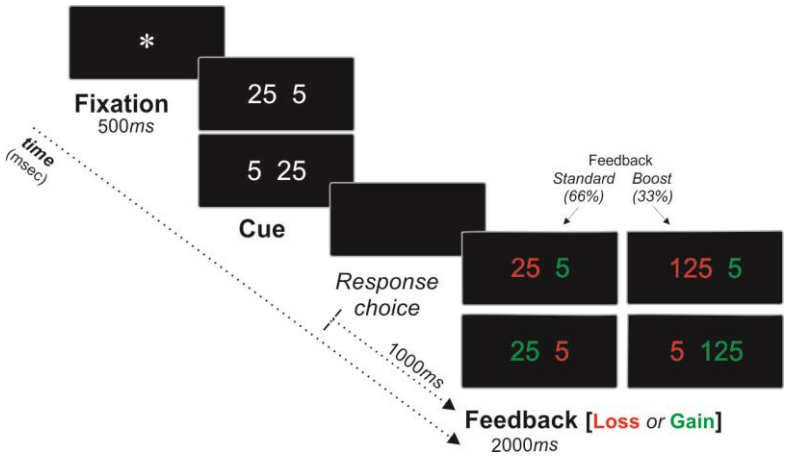

Figure 1. Gambling Task used in the experiment. After a fixation signal ("*"; 500 ms duration) two numbers appeared in the screen ([25][5] or [5][25]). Participants bet to one of two numbers (response choice). For instance in case of a [25][5] display, a left button press indicated the selection of the number 25, and a right button press the selection of the number 5. After the selection, one of the numbers turned red while the other turned green (feedback). If the number selected changed to red, the participant lost the corresponding amount in Euro cents, and vice versa. In 10% of trials, participants received unexpected feedback (boost gain or loss).

9.2.3. Procedure

MRI data acquisition. All subjects underwent a single MRI scanning session using a 1.5 Tesla GE Signa scanner (General Electric Medical Systems, Milwaukee, Wisconsin) located at Sant Joan de Déu Hospital in Barcelona (Spain). The session started with the acquisition of a high resolution T1-weighted image (TR=12.365 ms, TE=5.192 ms, flip angle 20º, slice thickness=1 mm, 0.468 mm in plane resolution, 190 slices, matrix size=512×512) in order to allow precise coregistration with functional data. After this, 2 runs of 300 sequential whole-brain Echo Planar Images sensitive to blood-oxygenation level-dependent contrast (Gradient Echo EPI; TR=2000 ms, TE=20 ms, flip angle 70º, slice thickness=6.5 mm, 3.28 mm in plane resolution, 23 slices, matrix size=64×64) were acquired.

fMRI preprocessing. Data were preprocessed using Statistical Parameter Mapping software (SPM8, Wellcome Department of Imaging Neuroscience, University

College, London, UK, www.fil.ion.ucl.ac.uk/spm/). The two functional runs were first realigned and a mean image of all the EPIs was created. The T1-weighted image was coregistered to this mean EPI image and then segmented into grey and white matter (GM; WM) by means of the New Segment toolbox included with SPM8 (Ashburner & Friston, 2005). Following segmentation, grey and white matter images were fed to DARTEL (Ashburner, 2007) in order to achieve normalization. After normalization, data was resampled to 2x2x2 mm^3 and spatially smoothed with an 8x8x8 full width at half maximum (FWHM) Gaussian kernel.

An event-related design matrix was specified using the canonical hemodynamic response function. Onsets for each condition were modeled at the moment in which participants received the feedback. Data were high-pass filtered (to a maximum of 1/128 Hz) and serial autocorrelations were estimated using an autoregressive (AR(1)) model. Motion effects were minimized by also including in the model the movement parameters estimated during the realignment phase. First-level contrasts were specified for all participants using each condition (gain, boost gain, loss, boost loss, blank) against the implicit baseline. The contrast images from all participants in the three groups were introduced into a mixed-design analysis of variance (ANOVA) with condition (gain, boost gain, loss, boost loss, blank) as a within-subjects variable and with Group (Healthy, NI-BPD, SI-BPD) as a between-subjects variable. A general gain (gain and boost gain) > loss (loss and boost loss) contrast for all groups (Healthy, NI-BPD and SI-BPD) was calculated to show the expected activations in reward-related areas (Camara et al., 2010). In addition, for each condition (gain, boost gain, loss, boost loss, blank) and for gain>loss and boost gain> boost loss the effect of Group was assessed with an F-test. Finally, for each condition showing a reliable Group effect,

two-sample t-tests (NI-BPD > Healthy, SI-BPD > Healthy, SI-BPD > NI-BPD and their respective reversed contrasts) were planned, to check for the direction of the effect.

All statistics in Figures and Tables are reported at a $p < 0.001$ uncorrected threshold with a minimal cluster size of 20 voxels (Lieberman & Cunningham, 2009). Peaks surviving a $p<0.05$ FWE-corrected threshold are indicated in tables. Maxima are reported in MNI coordinates. Anatomical and cytoarchitectonical areas were identified using the Automated Anatomical Label atlas (Tzourio-Mazoyer et al., 2002) and the Talairach Daemon database atlases (Lancaster et al., 2000) included in the xjView toolbox (http://www.alivelearn.net/xjview8/).

Functional-connectivity analysis. An exploratory connectivity analysis was also performed. An 8 mm radius ROI was defined around the peak value in left Orbitofrontal Cortex (OFC; -32 58 -14) of the F-test showing a Group effect for the boost gain condition (the only condition showing a significant Group effect, see Results below). Individual time-courses from this ROI were extracted, and an extended model was created, including the five conditions previously defined (gain, boost gain, loss, boost loss, blank) plus the extracted OFC time-course and the derived *psychophysiological interaction* (PPI) within the standard PPI approach (Friston et al., 1997) as regressors. PPIs were used to test for higher inter-regional coupling with the OFC during boost gains. Second level independent t-tests (NI-BPD > Healthy, SI-BPD > Healthy, SI-BPD > NI-BPD and the reversed contrasts) were computed.

For this exploratory connectivity analysis, a more lenient $p < 0.005$ uncorrected threshold with a minimal cluster size of 20 voxels, was used (Lieberman & Cunningham, 2009). Maxima and all coordinates are reported in MNI coordinates.

9.3. Results

Psychometric data. Psychometrical results are shown in Table 1. NI-BPD and SI-BPD groups were homogenous in terms of sensitivity to punishment and reward (SCSRQ), impulsivity (BIS-11) and aggression (AQ). In addition, both groups were homogenous in self-reported clinical severity (BSL-23). As expected, SI-BPD patients scored higher on the DIB-R than NI-BPD patients, as the impulsivity section is influenced by the presence of NSSI behaviors. Similarly, SI-BPD patients presented lower levels of general functioning (GAF) and of clinical severity than NI-BPD patients (considering clinical information).

fMRI contrasts. The general gain (gain and boost gain) > loss (loss and boost loss) contrast for all groups pooled together (Healthy, NI-BPD and SI-BPD) yielded activations in reward-related areas, especially in bilateral ventral striatum and bilateral orbitofrontal cortex (OFC; see Figure 2 and Table 2).

Regarding group comparisons, only the boost gain (which activated mainly bilateral orbitofrontal areas, see Table 3 and Figure 3A) yielded a significant Group effect (see first row of Figure 3B and Table 4 for the F-test contrast). Two-sample t-tests assessing the direction of the effect for boost gain trails showed enhanced activation in the bilateral OFC in SI-BPD patients compared to both healthy subjects and NI-BPD patients (see second and third row of Figure 3B and Table 4). Thus, SI-BPD patients showed an extreme activation of the OFC when presented with boost gains. Figure 3B (fourth row) shown an overlapping between all three groups. No other comparison yielded significant differences between groups.

Table 2. Effects of gains > losses

Anatomical area	BA	Coordinates	Cluster Size	t-value
Right Ventral Striatum; Right Putamen; Right Caudate.	-	20 14 -2	1295	5.20 *
Bilateral Cingulum; Bilateral Precuneus .	30, 31	2 -42 14	919	5.01*
Bilateral Cerebellum; Bilateral Inf. Temporal Gyrus, Bilateral Lingual gyrus; Bilateral Calcarine; Bilateral Cuneus; Bilateral Fusiform Gyrus; Bilateral Inf. Occipital Gyrus.	17, 18, 19, 20, 37	-38 -82 -22	5217	4.86 *
Left Ventral Striatum; Left Putamen; Left Caudate.	-	-16 12 -8	1086	4.71 *
Bilateral Medial Orbitofrontal Gyrus; Bilateral Superior Medial Frontal Gyrus; Left Anterior Cingulate Gyrus.	10, 11	-2 70 8	1677	4.56 *
Thalamus.	-	0 -14 10	185	4.25 *
Left Inf. Frontal Gyrus pars triangularis; Left Mid. Frontal Gyrus.	10, 46	-48 50 8	124	4.14

Effects of reward on regional fMRI-signal for all subjects (Healthy, NI-BPD and SI-BPD). Enhanced group level fMRI-signals for the gain && boost-gain > loss && boost-loss contrast thresholded at a $p < 0.001$ (uncorrected, extent threshold: k > 20 voxels; see also Fig. 2) using MNI coordinates.

*p<0.05 FWE-corrected at the peak level.

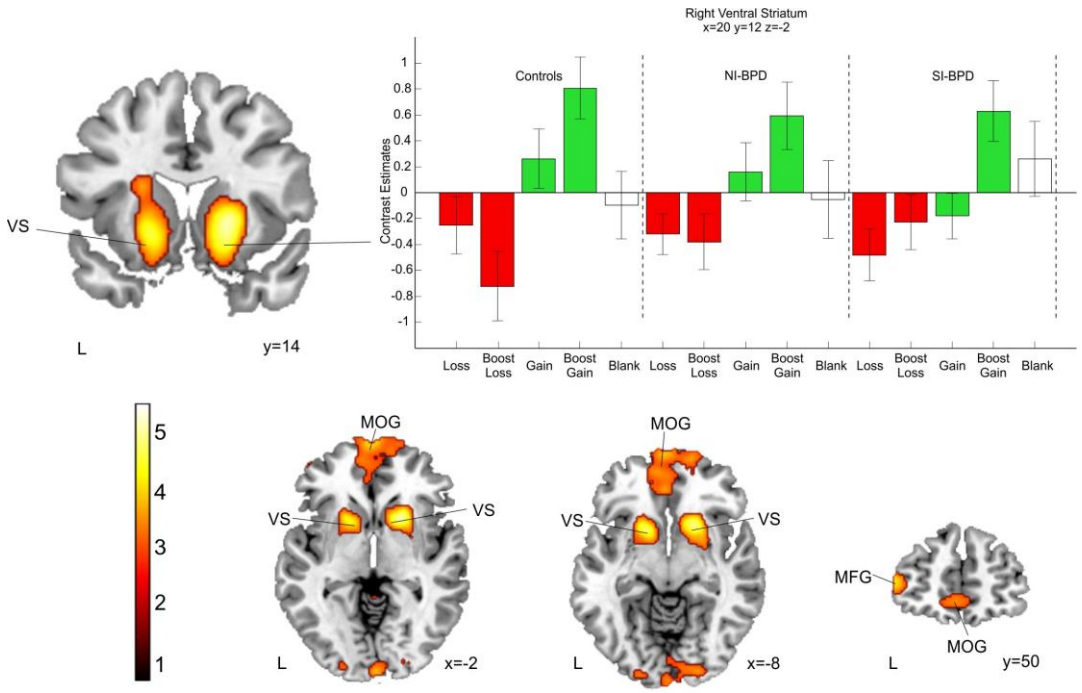

Figure 2. Enhanced group-level fMRI-signal for the general gain (gain and boost-gain) > loss (loss and boost-loss) contrast for all subjects (Healthy, NI-BPD and SI-BPD; p<0.001 uncorrected, k> 20 voxels). Bar graphs indicate contrast estimates (proportional to percent signal change; green: gain, red: loss, white: blank). Neurological convention is used with MNI (Montreal Neurological Institute) coordinates at the bottom right of each slice. VS, Ventral Striatum; MFG, Middle Frontal Gyrus; MOFC Medial Orbitofrontal Cortex.

For the functional connectivity analysis testing for higher inter-regional coupling with the OFC during boost gains, only the Healthy > SI-BPD patients contrast yielded significant differences at the right parahippocampal gyrus (*t*(38)=2.94, 29 voxels; 20 -24 -22; see Figure 3D). Therefore, SI-BPD patients compared to controls showed diminished functional connectivity between the left OFC and the right parahippocampal gyrus on the context of boost gains.

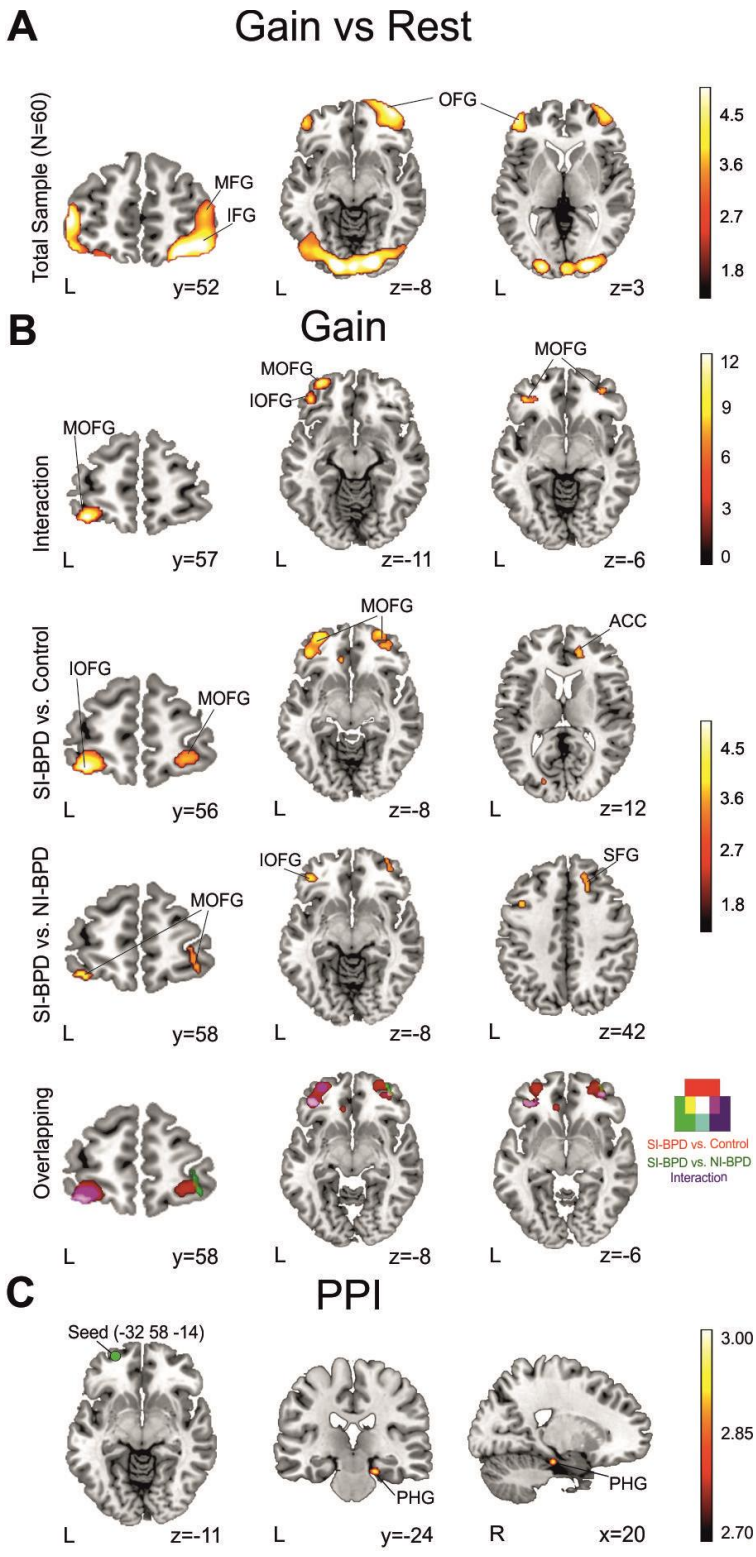

Figure 3. Neural correlates of reward processing for boost gain trials. Neurological convention is used with MNI coordinates at the bottom right of each slice (**a**) Boost Gain versus Rest contrast for all participants (Healthy, NI-BPD and SI-BPD; p<0.001 uncorrected). (**b**) Group effect for the Boost Gain trials (the only condition showing a reliable interaction, first row) with t-tests showing the enhanced activations at the OFC for the SI-BPD group > healthy controls (second row) and SI-BPD>NI-BPD (third row; all shown at a p<0.001 uncorrected threshold). Fourth row depicts the overlap between SI-BPD > healthy controls (red), SI-BPD>NI-BPD (green) and interaction (violet). (**c**) PPI analysis with the main peak at the left OFC used as seed (p<0.005 uncorrected). OFC, Orbitofrontal Cortex; IFGo, Inferior Frontal Gyrus *pars orbitalis*; MFG, Medial Frontal Gyrus; SFG, Superior Frontal Gyrus; PHG, Parahippocampal Gyrus.

9.4. Discussion

The present study investigated the reward system in a large sample of BPD patients and a matched control group. In a novel way, we divided 'a priori' the sample of BPD patients in function of the presence or not of NSSI behaviors (SI-BPD and NI-BPD respectively). As expected, the gambling task elicited strong activations in reward-related regions (especially in bilateral ventral striatum and bilateral OFC) in all participants (N=60), thus validating our paradigm. Group comparisons revealed that SI-BPD patients presented an enhanced activation in the bilateral OFC when compared to both healthy and NI-BPD participants. This sub-group of patients showed also diminished functional connectivity between the left OFC and the right parahippocampal gyrus when compared to healthy controls. Our results evidence, for the first time, alterations in the reward system of BPD patients as a function of the presence of NSSI behaviors.

During boost gain trials, compared to both healthy subjects and NI-BPD patients, the SI-BPD group presented an extreme activation of the OFC (BA 10, 11). This brain region is involved in higher-order cognitive functions (Ramnani & Owen, 2004) such as metacognition (Metcalfe & Shimamura, 1994) or the processing of internal states and emotions (Phan, Wager, Taylor, & Liberzon, 2002). Furthermore, the OFC has also been related with the processing of secondary reinforcers (such as money or social judgments) in contrast to more posterior prefrontal regions which seem to process more primary ones (sex or food) (Sescousse et al., 2013; Sescousse, Redouté, & Dreher, 2010b). In addition, alterations in this brain area underlie impairment in planning and reasoning, due to difficulties in the management and monitoring of sub-goals while maintaining information in working memory (Braver & Bongiolatti, 2002). Indeed, the

OFC has been shown to be active during a go/no-go task (Casey et al., 1997), therefore proving its role in the regulation of impulsivity, conflict resolution and inhibition. The present results, where SI-BPD patients showed alterations in reward processing at the level of the OFC, fit well with previous proposals of NSSI behaviors being regarded as dysfunctional emotional self-regulation methods (Nock, 2010): the enhanced activity in the OFC might point to an impairment in inhibitory control in the emotion regulation of SI-BPD patients (Ruocco, Amirthavasagam, Choi-Kain, & McMain, 2013). Thereby, we hypothesize that SI-BPD patients present a loss of inhibitory cognitive control which leads to impulsive, aggressive and self-destructive behaviors (i.e. NSSI).

Otherwise, OFC is also involved in the representation of the reward value of abstract reinforces (O'Doherty, 2004), playing an important role in the generation of reward expectations and predictions (Ramnani & Miall, 2003; Rushworth, Behrens, Rudebeck, & Walton, 2007) and thus guiding individuals' selection of advantageous over disadvantageous behaviour based on previous experience (Kringelbach & Rolls, 2004). Furthermore, the OFC has also been involved in reversal learning (Schoenbaum, Saddoris, & Stalnaker, 2007). It is important to emphasize that goal-directed actions are successful when they are rewarded; hence, the reward expectation must also influence systems concerned with action-planning and motor control (Ramnani & Owen, 2004). Most interestingly, here we used a gambling paradigm which requires constant reward predictions and subsequent switches in function of the random feedback. Therefore, present results evidenced that NI-BPD patients show alterations in the processing of abstract rewards as well as in the processing of unexpected positive gains for proper generation of reward expectations and predictions, partially in accordance with previous works of our group (Vega et al., 2013). In this line, the finding that the enhanced activity of the OFC in SI-BPD patients was in boost gain trials is congruent with

previous accounts which proposed that the unexpected occurrence of a reward (to receive a gain when it was not expected) elicited event-related changes in anterior prefrontal and OFC regions as well as, interestingly, in the parahippocampal gyrus (Ramnani, Elliott, Athwal, & Passingham, 2004).

Taken together, our findings complete previous fMRI studies which have evidenced reward system alterations in BPD (Enzi et al., 2013; Völlm et al., 2007). In particular, we show a clear dissociation in reward processing when comparing SI-BPD to NI-BPD patients. This result is in line with previous evidences of alterations in the reward pathways of BPD patients under negative emotional induction (Enzi et al., 2013), as NSSI behaviors are a self-regulation method (Klonsky, 2007). On the other hand, our results propose a central role of the OFC as an important region for NSSI behaviors. This is in accordance with previous studies which found decreased white matter microstructural integrity in the OFC in BPD patients with self-injurious behaviors (compared to healthy subjects) (Grant et al., 2007). In this line, reduced gray matter concentrations in OFC of BPD patients who committed suicide attempts compared to BPD non-attempters has also been found (Soloff et al., 2012). On the other hand, the hyperactivity found at the OFC in boost gain trials in SI-BPD patients could also be interpreted as a hypofunction at rest. In agreement with this, findings from PET studies found low orbitofrontal activity at rest in BPD patients (Soloff et al., 2003) whereas when performing an aggression induced task, BPD patients showed heightened relative glucose metabolic rate in the OFC (New et al., 2009). In addition, low resting levels of μ-receptors in orbitofrontal brain regions have also been shown in BPD patients (independently of the NSSI behaviors) in comparison to controls (Prossin, Love, Koeppe, Zubieta, & Silk, 2010). This evidence, together with our results, would support the idea that NSSI acts have a stimulating function of the (hypoactive) opioid

endogenous system in SI-BPD patients resulting in a decrement of negative affectivity, as it has been proposed in previous accounts (Bresin & Gordon, 2013).

The PPI analysis also revealed diminished functional connectivity between the left OFC and the right parahippocampal gyrus on the context of boost gains in the SI-BPD group (only in comparison to healthy participants). This is congruent with the hypothesis that the OFC is normally involved in executing behavior when reinforcement associations of environmental stimuli must be evaluated (Rolls, 2000). In addition, previous studies have proposed a dysfunctional connectivity between orbitofrontal and limbic regions in a BPD population (New et al., 2007), showing alterations in the processing and regulation of emotions (Ruocco et al., 2013). In this line, the parahippocampal gyrus is a part of the limbic system and it is mainly involved in encoding and retrieval information (Eichenbaum, 2000). It also plays a role in the processing of social and emotional contextual information (Rankin et al., 2009). Therefore, the diminished connectivity found might reflect an alteration in the integration (i.e. orbitofrontal cortex) of associative information and representational memory (i.e. parahippocampus) in SI-BPD patients. Thus, consistently with the NSSI phenomenology, during an emotional crisis (e.g. social adverse situation) the failure in the integration of associative memory could involve: i) incapacity to envision possible outcomes based on past experiences; ii) the inability to balance the desire for immediate gratification from self-harm with the recognition of the long-term consequences.

One plausible interpretation of present results is the consideration of NSSI as a possible behavioural phenotype of reward-related alterations in BPD patients. Thus it can be considered, from a conservative point of view, that alterations in this brain network in BPD patients is a continuum in which those SI-BPD patients are in the most severe extreme. On the other hand, an alternative interpretation is that this finding

supposes a biological evidence of two different BPD sub-groups (in function of the presence of NSSI behaviors), congruently to their clinical heterogeneity (Skodol et al., 2002). In this line, future research is necessary to study if reward-related alterations are maintained in other clinical groups or in non-clinical samples with NSSI behaviors, thus focusing on NSSI beyond categorical approach to mental disorders. Regarding treatment, the present findings open the door to individualized clinical treatment for different BPD patients; thus, most personalized approaches could be considered in function, for example, of the presence of NSSI behaviors. Furthermore, future studies are necessary to establish if NSSI behavior-remission as a result of BPD-specific psychological interventions (e.g. dialectic behavior therapy) is accompanied by reward-related changes such as improvement in the interpersonal attachment (see the introduction) or in OFC reward related activity. In this line, early treatment of young people with NSSI behaviors could be considered as an important tool for secondary and tertiary prevention.

A potential limitation of the present study arises from the uncontrolled co-morbidities, more specially the attention deficit hyperactivity disorder (Furukawa et al., 2014).

In sum, the present study supports previous findings showing reward related alterations in BPD (Enzi et al., 2013). However, here we evidenced that these alterations are highest in a sub-group of BPD patients who presented NSSI, in contrast to those patients who never engaged on this kind of behaviors. This important finding suggests, for the first time, that the alterations in reward processing are associated with NSSI and might be independent to overall symptoms in the BPD continuum. Concretely, due to enhanced activity in the OFC, SI-BPD patients might present impairment in reward-guiding behaviors and reward-based predictions in comparison to NI-BPD patients. In

addition, the reduced functional connectivity between the OFC and the parahippocampal regions further supports this claim, as impairment in the integration of associative information might also be present.

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Chapter III:

Study of Cognitive Control in the BPD [♣,♦]

[♣]Vega, D., Vilà-Balló, A., Soto, A., Amengual, J.A., Ribas, J., Torrubia, R., Rodriguez-Fornells, A., Marco-Pallarés, J. Preserved error-monitoring in Borderline Personality Disorder patients with and without non-suicidal self-injury behaviors (submitted).

[♦]Vega, D., Torrubia, R., Marco-Pallares, J., Soto, A., Ribas, J., Rodriguez-Fornells, A. Deficits in metacognitive monitoring of daily self-regulation processes in Borderline Personality Disorder patients (submitted).

10. Cognitive Control and NSSI: ERP approach.

Preserved error-monitoring in Borderline Personality Disorder patients with and without non-suicidal self-injury behaviors

10.1. Introduction

Borderline Personality Disorder (BPD) is the most common personality disorder, affecting about 0.5 to 5.9 % of the general population (Lenzenweger, Lane, Loranger, & Kessler, 2007). One of the most characteristic and common symptoms in BPD is the presence of non-suicidal self-injury (NSSI) behaviors (Zanarini et al., 2008a), which refers to the deliberate, self-inflicted destruction of body tissue without suicidal intent, and for purposes not socially sanctioned (*e.g.* tattoos or piercings) (Klonsky, 2007; Nock & Prinstein, 2004). Because NSSI behaviors are a public health concern (Klonsky, 2011), they have become a new clinical entity in the new DSM-5 (APA, 2013), in contrast to DSM-IV-TR (APA, 2000), in which they were only restricted to the BPD. Despite growing scientific interest, little is known about the reason why people engage in a direct form of self-injury against the innate fight for self-preservation (Nock, 2010).

BPD patients usually carry out NSSI behaviors during states of emotional stress as a maladaptive attempt to self-regulate (Linehan, Heard, & Armstrong, 1993; Linehan, 1987; Zanarini, Laudate, Frankenburg, Wedig, & Fitzmaurice, 2013). It has been proposed that these behaviors might be explained by a failure in the executive functioning involved in emotion regulation and cognitive control (Carpenter & Trull, 2013; Glenn & Klonsky, 2009). Dysfunction in executive processing might be at the core of some of the BPD symptoms, especially impulsivity and emotion regulation

among others (Mak & Lam, 2013), and has also been related with NSSI beyond the BPD (Fikke, Melinder, & Landrø, 2011).

One of the most important subcomponents of cognitive control is the capacity to monitor errors and conflicts associated with the performance of certain actions (also referred as 'response monitoring' or 'performance monitoring') (Ullsperger, 2006). A well-known electrophysiological signature of these functions is the Error-Related Negativity (ERN, also known as Ne) (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1990; Gehring, Goss, Coles, Meyer, & Donchin, 1993), an Event-Related Potential (ERP) which appears after the commission of an error in a speeded-up action-selection task. The ERN peaks 60-80 ms after the erroneous response and shows a frontocentral scalp distribution consistent with a neural source in the Anterior Cingulate Cortex (ACC) (Holroyd, Dien, & Coles, 1998). While the first accounts interpreted this component as error commission index (Gehring et al., 1993), recent theories have related it to different functions such as conflict detection (Yeung, Botvinick, & Cohen, 2004) or reinforcement-learning teaching signals indexing worse than expected events (Holroyd & Coles, 2002). In addition, another ERP component, the so-called error positivity Pe, appears around 300 ms after the commission of an error (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991). This ERP component shows a centro-parietal topography and has been related to error awareness (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001).

Error-processing dysfunctions have been reported in a variety of mental disorders when compared with healthy controls [for a review: (Manoach & Agam, 2013) and (Olvet & Hajcak, 2008)]. In the BPD, this alteration is manifested by an increase in the reaction time (RT) of erroneous responses compared to correct ones and attenuated

ERN (de Bruijn, Grootens, et al., 2006), but not Pe amplitude (Ruchsow et al., 2006). The reduced ERN amplitude has been related to self-reported impulsivity in these patients (Ruchsow et al., 2006). Surprisingly, no previous studies have investigated the ERP error monitoring signatures associated with the NSSI behaviors despite their relationship with executive functions. Thus, NSSI acts are impulsive (Dougherty et al., 2009; Jollant et al., 2005) and repetitive maladaptive coping responses to stressful situations (Klonsky, 2007), which suppose a non-optimal response to outcomes (Chapman, Gratz, & Brown, 2006). Due to overlapping between NSSI and BPD (69-90% of BPD patients engaged in NSSI) (Zanarini et al., 2008b), it is difficult to establish to what extent the impairment in error monitoring found in previous BPD studies (de Bruijn, Grootens, et al., 2006; Ruchsow et al., 2006) is specific to this disorder or, in contrast, is related to NSSI.

The goal of the present study was to determine the impairment of error monitoring and cognitive control in BPD patients according to their tendency to commit NSSI behaviors. Following previous studies we hypothesized that BPD patients (when compared to healthy controls) would present a reduced ERN after error commission indicating an impairment in cognitive control (de Bruijn, Grootens, et al., 2006; Ruchsow et al., 2006). In addition, we hypothesized that those BPD patients with NSSI history would show a larger reduction in ERN and Pe components compared to those without it, indicating a more severe impairment in the cognitive control system.

10.2. Methods

10.2.1. Participants

Two groups of 17 BPD outpatients each were selected. All patients were women, and were in treatment in the Mental Health Area of the Hospital of Igualada (Spain). Table 1 shows the demographical and clinical characteristics of these groups. The Diagnostic Interview for Borderlines-Revised (DIB-R) (Barrachina et al., 2004) was used two times with two independent, trained clinicians each, in order to ensure the diagnostic (first: 7.85±1.21; second: 7.82±1.26; Intraclass Correlation Coefficient =.58). The two groups were created according to the presence or not of NSSI. Thus, we selected a BPD group (SI-BPD; N=17) characterized by: a) lifetime history of five or more episodes of any NSSI behavior (determined by the Inventory of Statements About Self-injury, ISAS, see below), b) two of these episodes occurred in the last two years (determined by the self-harm item of the DIB-R). In contrast, the BPD group without NSSI (NI-BPD; N=17) was composed of BPD patients with no prior history of any NSSI behavior at the time of study enrollment (assessed by the ISAS and DIB-R). The NSSI typologies and frequency are depicting in Table 2. In addition the two groups were matched in sex, age and IQ (Table 1). Finally, seventeen sex-, age-, and IQ-matched control women, were recruited by means of local advertising. These participants have no previous history or current mental disorder.

All three groups were assessed with the Spanish adaptation of the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (Pérez-Prieto et al., 2008) and with DSM-IV Axis I interview (First & Gibbon, 1997). BPD patients showed comorbidity with other personality disorders [Avoidant (16.7%), Dependent (16.7%), Obsessive-Compulsive (11.1%) and Paranoid, Schizotypal, Histrionic and Antisocial (5.6% each one)], and Axis I disorders [Past: Major Depressive Disorder (38.9%), Eating Disorder (16.7%), any anxiety disorder (16.7%), Substance abuse (22.2%); Current: Posttraumatic Stress Disorder (22.2%), any other Anxiety Disorder (5-6%),

Eating Disorder (22.2.%), Substance abuse (27.8%) or other disorders (16.7%)]. The presence of brain injury, psychotic, bipolar, current major depressive disorder or drug abuse and IQ below 80 were exclusion criteria. All procedures were approved by the local ethical committee and written informed consent was obtained from all participants.

Table 1. Demographic and Clinical Characteristics of BPD patients and Healthy control participants

	NI-BPD (n = 17)		SI-BPD (n = 17)		Healthy Controls (n = 17)		Group differences	
	Mean	SD	Mean	SD	Mean	SD	*F*	*p*
Participants Characteristics								
Age (years)	30.29	6.26	29.94	6.04	33.18	.38	1.38	.261
IQ	101.08	10.06	94.96	8.19	99.52	.68	2.12	.131
Onset[a] (age)	27.06	5.01	25.47	5.21			.79	.378
Clinical status								
BIS-11	69	17.52	76.25	17.28	41.23	5.11	20.46	<.001[b]
HDRS	10.06	5.87	13.06	3.68			3.13	.087
GAF	56.04	7.98	47.96	6.84			-3.81	<.001
DIB-R	7.37	1.02	8.29	1.05			6.48	.016
CGI-BPD	4.51	1.41	5.65	0.99			7.32	.011
BSL-23	2.01	0.83	2.11	0.97			.33	.73

Notes. *BIS-11*, Barratt Impulsiveness Scale-11; *HDRS*, Hamilton Depression Rating Scales; *GAF*, Global Assessment of Functioning (DSM-IV); *DIB-R*, Diagnostic Interview for Borderlines-Revised; *CGI-BPD*, Clinical Global Impression for the BPD; *BSL-23*, Borderline Symptom List 23.

[a] Age at onset of any regular BPD treatment; [b] SI-BPD=NI-NSSI, BPD > Control.

10.2.2. Materials

Psychometric measures. Psychometric scales were used to evaluate different aspects of patients' symptoms and behavior. First, a Spanish version of the Inventory of statements about self-injury [ISAS: (Klonsky & Glenn, 2008)], was used to quantify

lifetime frequency of 12 NSSI behaviors (*e.g.*, cutting, burning, carving) and their descriptive and contextual factors (*e.g.*, age of onset). This part of the ISAS shows good reliability and validity (Glenn & Klonsky, 2011). Those respondents who endorsed one or more NSSI behaviors were instructed to complete the second part of the ISAS, which assesses 13 potential functions of these NSSI behaviors (e.g. sensation seeking, affect regulation). Participants also completed the Borderline Symptom List [BSL-23: (Bohus et al., 2009), Spanish version: (Soler et al., 2013)] which evaluates the amount of suffering on a list of 23 problems during the last week (e.g., "It was hard for me to concentrate" or "I wanted to punish myself"). In addition the CGI-BPD severity form scale, which is an adaptation of the Clinical Global Impression (CGI) scale designed to assess severity in BPD patients (Perez et al., 2007), was completed by the clinician. Finally, the Barratt Impulsiveness Scale (BIS-11) (Patton, Stanford, & Barratt, 1995) was used to measure the impulsivity of the patients.

Medication load. A medication load protocol was used to determine the total medication load, as previously used in psychiatric population (Vederman et al., 2012). Anti-depressant, anxiolytic, mood stabilizer, and anti-psychotic medications were coded as absent = 0, low = 1, or high = 2 based on previously employed methods to convert each medication to a standardized dose (Almeida et al., 2009; Sackeim, 2001). Anti-psychotics were converted into chlorpromazine dose equivalents (Davis & Chen, 2004). As a result, a composite measure of total medication load was obtained.

Table 2. Lifetime frequency of 12 NSSI behaviors assessed by the ISAS.

	NSSI behaviors											
	cutting	burning	scratching	banging	biting	carving	wound picking	needle-sticking	pinching	hair pulling	Rubbing [a]	Chemicals [b]
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
<5	3 (17.6)	5 (29.4)	15(88.2)	11 (64.7)	12 (70.6)	10 (58.8)	12 (70.6)	2 (11.8)	7 (41.2)	10 (58.8)	16 (94.1)	15 (88.2)
5-50	6 (35.3)	7 (41.2)	1 (5.9)	4 (23.5)	3 (17.6)	3 (17.6)	3 (17.6)	9 (52.9)	4 (23.5)	3 (17.6)	1 (5.9)	1 (5.9)
51-100	1 (5.9)	2 (11.8)	0	0	0	2 (11.8)	2 (11.8)	2 (11.8)	2 (11.8)	1 (5.9)	0	0
101-250	2 (11.8)	1 (5.9)	1 (5.9)	0	0	0	0	1 (5.9)	2 (11.8)	2 (11.8)	0	0
>250	5 (29.4)	2 (11.8)	0	2 (11.8)	2 (11.8)	2 (11.8)	0	3 (17.6)	2 (11.8)	1 (5.9)	0	1 (5.9)
Total > 5	14 (82.4)	12 (70.6)	2 (11.8)	6 (35.3)	5 (29.4)	7 (41.2)	5 (29.4)	15 (88.2)	10 (58.8)	7 (41.2)	1 (5.9)	2 (11.8)

BPD subjects estimated the number of times they have engaged NSSI behaviors. The total score was grouped in different categories (from less than 5 times to more than 250 times). Additionally the lifetime frequency above 5 for each NSSI type was computed.

[a] Rubbing skin against rough surfaces

[b] Swallowing chemicals

Task. We applied a modified variant of the Eriksen flanker task (Eriksen & Eriksen, 1974) that required the participants to respond, using the index finger of each hand, to the pointing direction (right or left) of a central arrow from an array of five arrows. All four surrounding arrows were either compatible or incompatible with the central arrow (same or different direction respectively), favoring performance errors in the incompatible condition (Krämer et al., 2007; Rodriguez-Fornells, Kurzbuch, & Münte, 2002). We presented 33.3% of compatible and 50% of incompatible trials. In the remaining 16.6%, we included no-go trials, following a variant of the stop-signal paradigm (Band, van der Molen, & Logan, 2003). In these stop trials, the central green arrow changed to red after a variable delay, indicating that participants should inhibit their response. The delay was adapted to participants' behavior by means of a staircase tracking algorithm (Band & van Boxtel, 1999) as follows. The stop-signal delay was set to 140 ms initially. After a successful inhibition the stop-signal delay was increased by 10 ms (making the inhibition harder). After an inhibitory failure the stop-signal delay was reduced by 10 ms (making inhibition easier). This procedure was applied to yield an inhibition rate of 50%.

We computed the stop-signal reaction time (SSRT) (Band et al., 2003) by subtracting the participant's mean stop-signal delay from the median reaction time of correct go responses. Each stimulus array was presented in the middle of the screen. Stimulus duration was 300 ms and the stimulus onset asynchrony was fixed to 900 ms. Participants received 20 training trials to get acquainted to the task. They were encouraged to correct their errors in the go trials as fast as possible. The experiment was divided into eight blocks, each comprising 240 trials, resulting in a total of 1920 trials.

10.2.3. Procedure

Electrophysiological Recording. The electroencephalographic (EEG) activity was recorded continuously (digitized with a sampling rate of 250 Hz, high-pass band at 0.01 Hz, notch filter) using SYNAMP Neuroscan amplifiers from 28 tin electrodes, mounted in an elastic cap and located at standard positions (FP1/2, F3/4, C3/4, P3/4, FCz, T3/4, F7/8, T5/6, Fz, Cz, Pz, FC1/2, FC5/6, CP1/2, CP5/6, PO1/2). The EEG was referenced on-line to the right ocular canthus. Biosignals were re-referenced offline to the mean of the activity at the two mastoid processes. Electrode impedances were kept below 5 kΩ. Vertical eye movements were monitored by an electrode placed below the right eye.

10.2.4. Data analysis

ERP averages were also obtained for the different conditions (time-range from -100 to 924 ms for stimulus-locked averages and from -400 to 600 ms for response-locked ERPs). In the stimulus-locked ERPs we included a baseline period of 100 ms prior to the stimulus and for the response-locked the baseline was 50 ms before the button press. Epochs exceeding ±100 μV in electrooculogram (EOG) or EEG were removed from further analysis. In the behavioral and ERP analyses only reaction time (RT) responses that were produced between 120-750 ms after the stimulus were considered (Gehring, Coles, Meyer, & Donchin, 1995). All artifact-free error trials were included regardless of a subsequent corrective response. To increase the number of error trials, we included choice-errors and stop-errors together in the ERP analysis.

For statistical analysis of the stimulus-locked and response-locked epochs we defined specific time-windows considering a previous study (Rodriguez-Fornells et al.,

2002). ANOVAs with Condition (compatible, incompatible), Electrode location (Fz, Cz, Pz) and Response (correct, incorrect), as within-subject factors and Group (Control, SI-BPD and NI-BPD) as between-subject factors were performed using the Greenhouse-Geisser epsilon correction as appropriate (Jennings and Wood 1976). The corrected *P*-value is reported. Finally, to discard possible effects of medication, medication load value was included as a covariate (Med_Load) in the previous ANOVA.

Time-Frequency of the electrical activity elicited by the errors and the correct responses were generated (epochs comprising 4000 ms; 2000 ms before and after the response). Epochs exceeding ±100 μV in EOG or EEG were removed from further analysis. Baseline was the 100 ms prior the button press. Single trial data was convoluted using a 7-cycles complex Morlet wavelet (Tallon-Baudry, Bertrand, Delpuech, & Permier, 1997). Changes in time varying energy (square of the convolution between wavelet and signal) in the studied frequencies (from 1Hz to 40Hz; linear increase) with respect to baseline were computed for each trial and averaged for each subject before performing a grand average.

10.3. Results

Psychometric results. The psychometric results are depicted in Table 1. As it shows, the SI-BPD group obtained a higher overall score than the NI-BPD group in the diagnostic interview (DIB-R). Congruently, the severity indices showed higher severity (CGI-BPD) and less functionality (GAF) of SI-BPD than NI-BPD group. Contrarily, both groups did not show statistical differences in current depressive symptoms (HDRS) or in the self-reported measures of clinical state (BSL-23) and impulsivity (BIS-11).

Behavioral results. Participants responded faster to compatible (451.50 ± 61.77 ms) than to incompatible (478.97 ± 60.56 ms) trials (main effect of Condition, $F(1,48) = 160.6$, $p < .001$). Importantly, no significant differences were found between groups (Group: $F(2,48) = 1.2$, $p = .300$; Condition x Group: $F(2,48) = 1.8$, $p = .170$; See Fig. S1a in the Supplemental material of the Appendix).

No statistical differences were found between groups in the percentages of correct trials and correction after errors ($F<1.7$). Furthermore, importantly, no SSRT differences were found between groups. In consequence, the three groups were showed very similar in their behavioral performance in the Flanker task (see for a detailed analysis of behavioral data Table S1 and Fig. S1 in the appendix).

Response-locked ERP data. Errors led to an increased negativity peaking about 50 ms after the error (see Figures1and 2), which was identified as the ERN component, with a clear fronto-central scalp distribution in all groups (Falkenstein et al., 1991; Gehring et al., 1993). A repeated measures ANOVA (rmANOVA) including Group (Control, SI-BPD and NI-BPD) as a between-subject factor and Response (Correct *vs*. Error) and central Electrodes (Fz, Cz, and Pz) as within-subjects factors (mean amplitude measured at the time-window 30-80 ms) was performed. The increased negativity after errors, that characterizes the ERN component, was confirmed by the significant main effect of the Response [$F(1,48)= 25.8$, $p < .001$]. However, unexpectedly considering previous findings in the literature, no significant group differences were observed [Group: $F(2,48)= .2$, $p = .815$; Response x Group: $F(2,48)= .252$, $p = .778$]. Figure 3 shows the distribution of the ERN values for all the subjects of the three groups. As can be seen, the distribution in the three groups is very similar, except for a subject presenting a very high ERN value in the NI-BPD group. However,

if the rmANOVA is repeated excluding this participant results are the same, showing no significant differences among groups [Group: $F(2,47)= .814$, $p = .449$; Response x Group: $F(2,47)= .247$, $p = .782$].

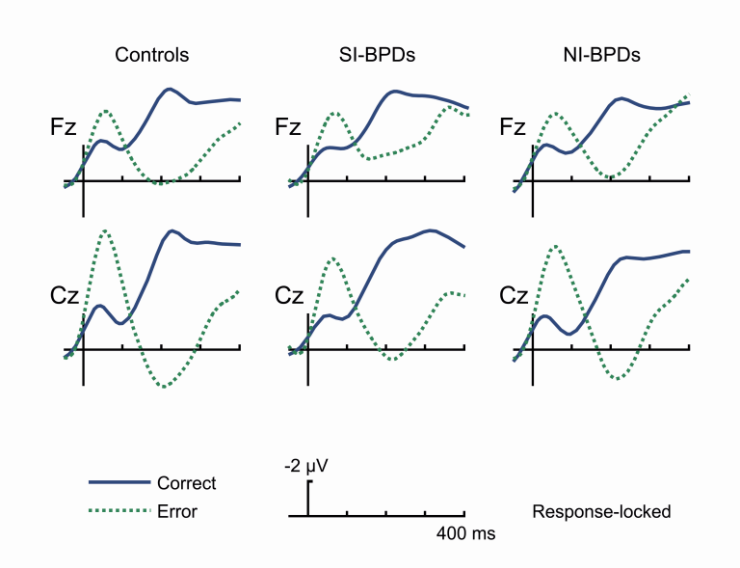

Figure 1. Grand average of response-locked ERPs at Fz and Cz electrodes for controls, SI-BPD and NI-BPD individuals. Correct trials are depicted in blue solid lines, and choice/stop-error trials in green pointed lines. Data were low-pass filtered at 12 Hz for illustration purposes.

The Pe ERP component peaked around 200 ms (Figures 2 and 3).We conducted the same rmANOVA analysis as for the ERN using the mean amplitude measured at the time-window 185-265 milliseconds. The Pe was associated with errors trials as shown by a Response main effect [$F(1,48)= 95.598$, $p < .001$]. Visual inspection suggested a reduction of the Pe in SI-BPD group compared to the Control group and the NI-BPD group. However, no significant main effect of Group [$F(2,48) = .393$, $p = .677$] nor interaction Response x Group [$F(2,48) = .818$, $p = .448$] were found, showing no differences between groups in this ERP component. As can be observed in Figures 1 and 2, the amplitude of the Pe component considering the previous ERN peak seems to be reduced in BPDs groups, especially in the SI-BPD group. Nevertheless, we calculated the difference in amplitude between the ERN and the Pe peaks in the error trials for all subjects at Cz electrode, and discarded a reduced ERN-Pe amplitude for

BPDs by means of an ANOVA analysis with Group as single factor [$F(2,48) = .825$, $p = .444$]. Figure 3 also shows the distribution of Pe amplitudes for the three groups.

Finally, in order to discard the possibility of significant differences existing between groups in the ERPs of different frequency domains (Bernat, Nelson, Steele, Gehring, & Patrick, 2011) we repeated the same analysis filtering the data to delta (1-3 Hz) and theta (3-9 Hz) frequency bands (Figure 4A). The rmANOVA revealed neither significant differences between groups [(SI-BPD, NI-BPD, Control) and (BPD, Controls)] nor congruently with non-filtered results (see supplementary results in the appendix for details).

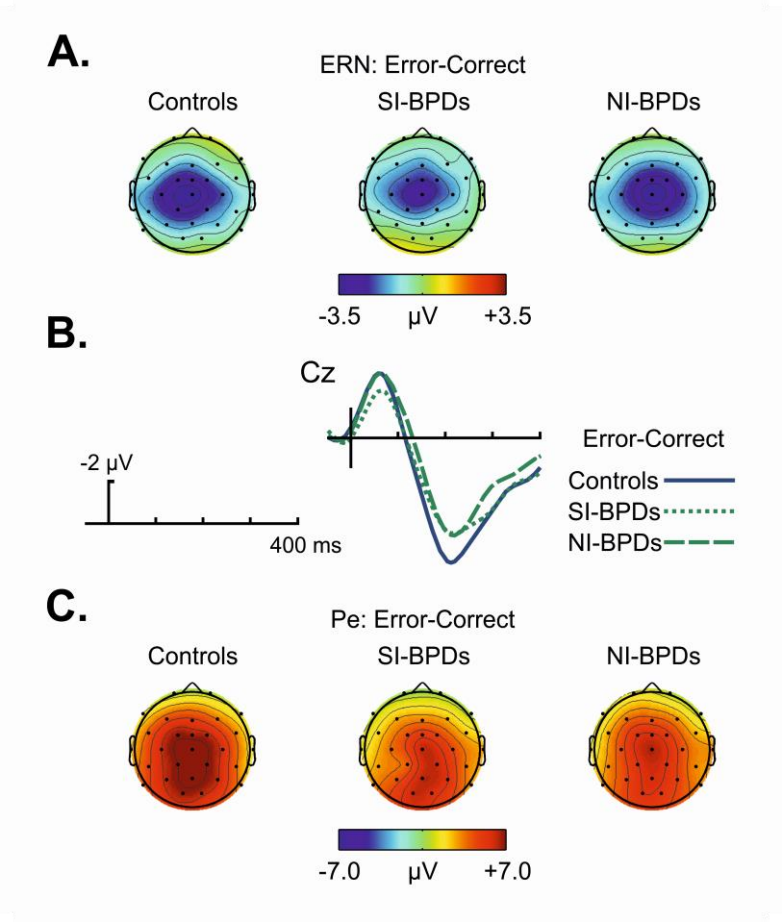

Figure 2.A. Topography for error *vs* correct for the time window 20-70 ms (maximum and minimum values in microvolts are -3.5 and +3.5). B. Differences waveform for the grand average between the error and correct trials, at Cz electrode, for controls (blue solid line), SI-BPD (green pointed line), and NI-BPD (green dashed line) individuals. C. Topography for error *vs* correct for the time window 170-270 ms, maximum and minimum values in microvolts are -7.0 and +7.0.

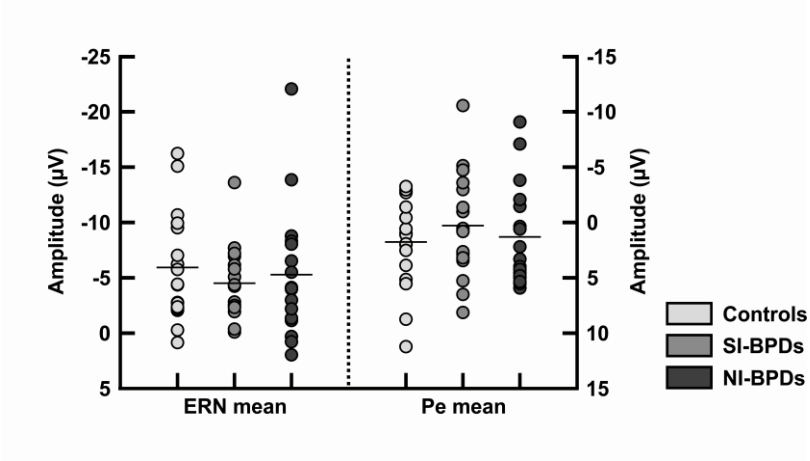

Figure 3. Mean amplitude distribution of the ERN and Pe for each participant, divided into the three groups of study (Controls, SI-BPD and NI-BPD). A clear overlapping of distributions can be seen.

Time-Frequency: response-locked data. In order to study the effects in the power of theta band associated with error commission (see Figure 4B), a rmANOVA including Group (Control, SI-BPD, NI-BPD) as a between-subject factor and Response (correct *vs.* error responses) and central Electrodes (Fz, Cz, and Pz) as within-subjects factors (mean amplitude measured at the time-window 50-250 ms) was performed. The significant main effect of Response [$F(1,48) = 147.879$, $p < .001$] confirmed larger theta power for the error trials compared to the correct trials. As in the ERP analyses, no group differences were found between groups [Group: $F(2,48) = .444$, $p = .644$; Response x Group: $F(2,48) = 1.988$, $p = .148$]. We also conducted different exploratory rmANOVA analysis with narrow time-windows in the 50-250 ms time range, but in all of them we found similar, statistically insignificant differences between groups.

Medication load. The medication load effects were tested both for ERPs and for the theta band power of Time-Frequency. First, the ANCOVA analysis revealed no main effect of MedicationLoad for the ERN [$F(1,30) = .369$, $p = .548$] nor the Pe components [$F(1,30) = .550$, $p = .464$]. Second, the ANCOVA analysis also revealed no

main effect of Medication Load for the theta band power of Time-Frequency [$F(1,30) = .736$, $p = .398$, see supplementary information in the appendix for additional results].

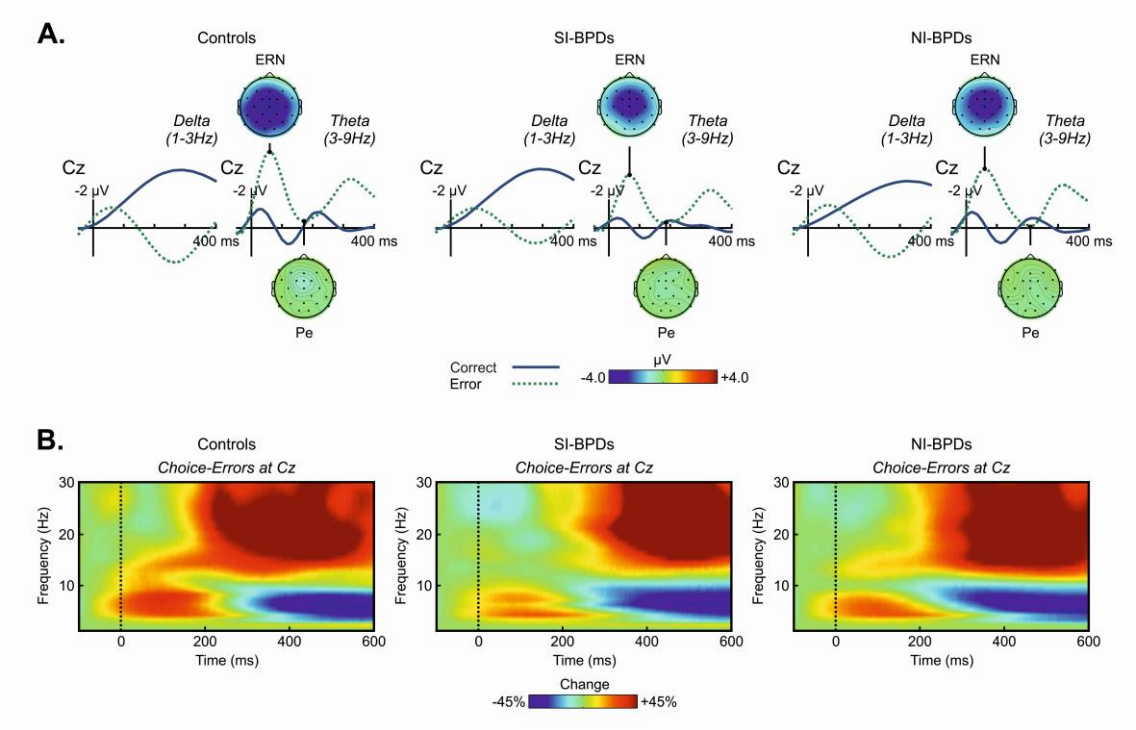

Figure 4. A. Grand average of response-locked ERPs at Cz electrode, filtered for delta activity (3hz low pass), and for theta activity (3-9hz band pass), for controls, SI-BPD and NI-BPD individuals. Correct trials are depicted in blue solid lines and error trials in green dashed lines. Scalp distribution for theta (3-9hz band pass filter) error activity were calculated for the two time windows 55-75 ms (ERN), and 170-220 ms (Pe), maximum and minimum values in microvolts are -4.0 and +4.0. B. Grand average of spectral power modulation for the error trials at Cz electrode.

10.4. Discussion

In the present manuscript we studied whether a large sample (N = 34) of well characterized BPD patients presented an executive dysfunction in error monitoring and if this problem could be associated with non-suicidal self-injury (NSSI) behaviors. The results showed very clearly that neural signatures of error processing (ERN, Pe and theta oscillatory activity) were not altered in BPD patients compared to healthy controls. In addition, no significant differences in behavioral measures of error rates, reaction

time and corrective actions after the commission of an error were found. These results are contrary to our hypothesis formulated based on previous findings (de Bruijn, Grootens, et al., 2006; Ruchsow et al., 2006) and suggest preserved error monitoring mechanisms in BPD patients, independent of their NSSI behaviors.

Present findings contradict previous evidences which showed alteration of error monitoring in these patients when compared with healthy controls, especially a reduction in the ERN component amplitude (de Bruijn, Grootens, et al., 2006; Ruchsow et al., 2006). Moreover, in contrast to previously report by Ruchsow et al. (2006), we did not find alterations in the Pe component or reaction times respecting control participants. Additionally, although patients self-reported higher impulsivity than control participants, the behavioral performance on the Flanker task was similar between patients and controls and no significant differences were found in the inhibitory measures related to the stop signal (SSRT and post error slowing differences). These differences regarding the two previous studies (de Bruijn, Grootens, et al., 2006; Ruchsow et al., 2006) might be explained by the higher number of participants included in the present one (34 BPD *vs* 12 BPD patients in the two previous studies). In this vein, the lack of alteration in error monitoring in BPD patients obtained here, is in convergence with previous inconsistent findings concerning executive functions in BPD (LeGris, Links, van Reekum, Tannock, & Toplak, 2012). These last results suggest that BPD executive functions are preserved in all sub-domains, except in working memory (Hagenhoff et al., 2013). Complementarily, Hagenhoff et al. (Hagenhoff *et al.* 2013) did not find impairment in response inhibition nor error rates in BPD patients, which is also evidenced in the present paper. Thus, as proposed by others (Krause-Utz et al., 2013; Lampe et al., 2007), response inhibition deficits might not be a core aspect in BPD at least considering standard laboratory measures as for example, the stop-signal task.

A novel approach of this study was the inclusion of two groups of BPD patients, one with NSSI history and another without. Despite BPD patients who engage in NSSI behaviors showing high clinical severity and functional impairment (in comparison with NI-BPD group, as shown in DIB-R, CGI-BPD and GAF scores), behavioral measures (except reaction time for erroneous responses), ERN and Pe amplitudes and theta power increase were similar in these two groups of patients. Thus, beyond the possible impact of NSSI behaviors in everyday life, BPD patients who self-harm, have preserved error monitoring mechanisms when compared with healthy controls and BPD patients without history of NSSI behaviors. In this same line, Janis and Nock (Janis & Nock, 2009) reported no differences in performance-based measures of impulsiveness in NSSI individuals, showing that they are, perhaps, impulsive only in certain situations. Indeed, BPD patients have shown alterations in their fronto-limbic neural activity patterns, during the performance of behavioral tasks under negative emotional induction [*e.g.* verbal salient stimuli in a go/no-go task, (Silbersweig et al., 2007); performing a go/no-go task after anger induction, (Holtmann et al., 2013)].

Therefore, given this finding, NSSI behaviors could not be explained by a dysfunction in error monitoring. This is congruent with the idea that these behaviors respond to a variety of functions and, importantly, that not all self-injurers engaged in this behavior act impulsively and "out of control" [that is, associated with a lack of executive control: (Herpertz, Sass, & Favazza, 1997; Herpertz, 1995)], but they might spend some time thinking about NSSI before engaging in it as an emotional self-regulation strategy (Chapman et al., 2006; Klonsky, 2007; Nock, 2010). Consequently, to understand why these complex behaviors are maintained (which is very interesting because they are not an isolated act), is important to consider that BPD patients would incur in NSSI behaviors not as a consequence of a systematic failure in the internal error

signals processing (ERN, Pe), but because their contingencies are reinforced [*e.g.* feel alive, stop arguing, (Nock, 2010)]. This hypothesis is congruent with Linehan's biosocial theory (Crowell, Beauchaine, & Linehan, 2009), insomuch as the NSSI behaviors are maladaptive attempts to self-regulate negative emotional states which, in turn, are positively and/or negatively reinforced by their outcomes. It is important to notice that because of their preserved error monitoring system, the learning of alternative self-regulating strategies (more adaptive than NSSI) is possible in most BPD patients who undergo a psychological treatment (Linehan, Armstrong, Suarez, Allmon, & Heard, 1991; Linehan, 1987), showing that they are able to process the internal error signals adequately, in contrast to the external feedbacks (King-Casas et al., 2008; Schuermann, Kathmann, Stiglmayr, Renneberg, & Endrass, 2011; Vega et al., 2013).

The main limitation of the present study arises from the fact that BPD patients included were undergoing psychopharmacological treatment. Despite being ecologically valid, it is known that the psychopharmacological compounds could play a confounding effect on the ERN (de Bruijn, Hulstijn, Verkes, Ruigt, & Sabbe, 2004; de Bruijn, Sabbe, Hulstijn, Ruigt, & Verkes, 2006). Importantly, we used a medication load scale which showed no relationship between behavioral and electrophysiological measures. Another potential limitation of the present data arises from the uncontrolled co-morbidities, more specially the ADHD which were related with deficits in executive functions (Lampe et al., 2007; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Finally, all participants were females and, in consequence, the present results cannot be generalized to males due to the gender differences in executive functioning (Bolla, Eldreth, Matochik, & Cadet, 2004) and in the ERN component (Moran, Taylor, & Moser, 2012).

In summary, present results show that error monitoring mechanisms are not a core aspect of BPD or NSSI behaviors. Therefore, in an attempt to self-regulate, the NSSI are not impulsive behaviors associated with the failure of a primary mechanism in performance monitoring, but with more complex interactions (*e.g.* information processing distortion, long lasting traits, emotional avoidance patterns). These results are encouraging because they show that BPD patients are able to detect, monitor and inhibit these behaviors. They also allow a better understanding of these complex and disabling behaviors, which are a public health concern and pose a therapeutic challenge.

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11. Cognitive Control: Metacognition approach.

Deficits in metacognitive monitoring of daily self-regulation processes in Borderline Personality Disorder patients

11.1. Introduction

A core aspect of Borderline Personality Disorder (BPD) is the lack of appropriate self-regulatory mechanisms (*e.g.*, strong emotional dysregulation, behavior outbursts) most often manifesting in daily social contexts (King-Casas et al., 2008; Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004). This aspect has been associated to deficits in both the ability to envision the mental states of others based on interpersonal cues (mentalization) and in the use of social-feedback information to appropriately control their behavior (Bateman & Fonagy, 2004; Fonagy & Target, 2006). These social-feedback signals are crucial for the correct construction of one's self-image (Diehl & Hay, 2007). It has also been reported that BPD patients show problems in self-image reconstruction, showing non-reflective, contradictory and chaotic descriptions of themselves (and others), a lack of awareness of their conflict appraisals (Kernberg, 1967) and problems in correctly processing emotional-related feedback (Vega et al., 2013). Despite this interesting relationship between self-image processes and self-regulation mechanisms in real-life social situations, there is a lack of research on this topic in BPD patients.

Interestingly in recent years, cognitive neuroscience has paid much attention to the study of higher-order self-reflective cognitive processes that may be used for regulating information processing and for evaluating one's cognition and behavior (i.e. *metacognitive processes*) (Flavell, 1979). This metacognitive capacity is involved in the monitoring (e.g. performance predictions) and control (e.g. error correction) of multiple

daily tasks (Nelson & Narens, 1994). Moreover, it involves mental representations of one's self-image (Lyons & Zelazo, 2011) and is crucial for self-regulation learning (Ridley, Schutz, Glanz, Weinstein, & Taylor, 2011), self-confidence or self-efficacy perceptions (Kleitman & Stankov, 2007). Much research has implicated the prefrontal cortex (PFC) regions in metacognitive processing (Fernandez-Duque, Baird, & Posner, 2000). Indeed, a decrease in metacognition (i.e. judgments of performance), without affecting task performance, has been observed when disrupting the dorsolateral PFC with transcranial magnetic stimulation (Rounis, Maniscalco, Rothwell, Passingham, & Lau, 2010). Interestingly, performance of a particular cognitive task and metacognition of the performance are usually tightly coupled (i.e. metacognitive accuracy) and is also attuned to what others may observe (Nelson & Narens, 1994).

The aim of this study was to evaluate for first time to our knowledge, metacognitive abilities of a BPD sample in relation to self-regulatory and cognitive control mechanisms. We used an innovative methodology that allowed us to measure self-regulatory processes in daily-life activities and to compare self-image evaluations with external perceptions of the patients' self-regulatory abilities by close relatives (paired informants). Due to the problems associated with mentalization and the incapacity to correctly infer information from social interpersonal cues, we predicted that BPD participants would show monitoring deficits (low metacognitive accuracy) in their self-regulation abilities used in everyday functioning. We contrasted these results on metacognition of self-regulation to the capacity of BPD patients to accurately estimate their long-lasting personality traits, based on previous studies which showed higher self- and hetero- report concordance in BPD patients than in those with other personality disorders (Klonsky, Oltmanns, & Turkheimer, 2002). This also allowed us

to evaluate the generalization of these findings and to compare this to other domains in which patients need to correctly monitor autobiographical or self-referential memories.

Finally, we assessed to what extent this deficit would be related to functional and clinical BPD severity indexes. The most important finding of this study is that we identified a robust but isolated negative bias of BPD patients in the evaluation of their metacognitive self-regulatory capacity, which did not generalize to other self-image domains (long-lasting personality traits).

11.2. Method

11.2.1. Participants

Participants were recruited from the Borderline Personality outpatient treatment program of the Hospital of Igualada (Barcelona, Spain) and via a local advertisement for healthy volunteers. The study involved 144 participants divided in pairs of respondents (72 self-informing participants and their corresponding 72 informants made up of close relatives). Of the self-informant participants the sample consisted of 36 BPD and 36 healthy controls, all females and matched by age and intelligence (IQ) (see Table 1). The BPD diagnosis was confirmed using the Structured Clinical Interview for DSM-IV Axis II (SCID-II) and the Diagnostic Interview for Borderlines-Revised (DIB-R) (Barrachina et al., 2004). In addition they were assessed with the SCID-I. The presence of brain injury, psychotic, bipolar or current major depressive disorders, drug abuse or an IQ below 80 were all exclusion criteria. Healthy participants had no historical or current mental disorders.

Table 1. Demographical and clinical characteristics of participants (BPD and Control groups), and relevant data of informants [a]

	BPD (n=36)		Control (n=36)		Analysis	
	Mean	SD	Mean	SD	*t*	*p*
PARTICIPANT						
Age (years)	32.03	7.15	29.17	6.05	1.83	0.072
Education (years)	15.75	3.07	18.66	1.26	-5.26	<0.001
IQ	96.86	9.78	98.05	8.54	-0.61	0.545
DIB-R	7.67	1.06				
GAF	50.22	8.41				
CGI-BDP	5.25	1.41				
HAM-D	10.91	4.49				
Medication Load	2.77	2.58				
	N	%				
Current comorbidity[b]						
Any Anxiety Disorder	11	30.6				
Eating Disorder	11	30.6				
Drug Abuse	10	27.8				
Other[c]	10	27.8				
Past comorbidity						
MDD	15	41.7				
Any Anxiety Disorder	7	19.4				
Eating disorder	7	19.4				
Drug abuse	12	33.3				
Axis II comorbidity						
Avoidant	5	13.9				
Dependent	9	25				
Ossesive-Compulsive	2	5.6				
Paranoid	4	11.1				
Eschizotypical	2	5.6				
Antisocial	6	16,7				
	Mean	SD	Mean	SD	*t*	*p*
INFORMANT						
Years of relationship	20.89	12.84	18.06	10.01	1.04	0.301
	N	%	N	%	χ^2	*p*
Sex (male)	16	44.4	22	61.1	2.01	0.157
Currently living together	23	63.9	19	52.8	0.91	0.339
Relationship						
Father/mother	12	33.3	9	25	1.47	0.479
Partner/spouse	12	33.3	17	47.2		
Other[d]	12	33.3	10	27.8		

[a] IQ=Intelligence Quotient; DIB-R= Diagnostic Interview for Borderlines Revised; GAF= Global Assessment of Functioning Scale; CGI-BPD=Clinical Global Impression-BPD; HAM-D=Hamilton Depression Rating Scale. MDD = Major Depressive Disorder

[b] Comorbid disorders were assessed with SCID-I and SCID-II

[c] This category includes, for example: adaptive disorder or distimic disorder

[d] Includes other levels of relationship such for example sibling or cousin

All participants were informed about the purpose of the study. All procedures were approved by the local ethical committee and written informed consent was obtained from all participants.

11.2.2. Procedure

The assessment of participants was carried out in facilities at the Hospital of Igualada. Each self-informing participant answered the questionnaire about themselves and their close-relative informant separately answered the questionnaire about their corresponding self-informant. The informants gave their impressions of the target participant under confidentiality. In those cases where close-relatives were unable to attend, a packet with clearly written instructions about the procedure was provided to the self-informants to give to their paired informant. Researchers then contacted the hetero-informants (i.e. the close-relative) by telephone in order to verify that the instructions were understood and that they were followed correctly. Any questionnaires which did not meet the validity scales criteria were excluded.

11.2.3. Materials

Psychometric measures. The Behavior Rating Inventory of Executive Function-adult version (BRIEF-A) (Roth, Isquith, & Gioia, 2005) is a standardized 76 item self-report measure that captures an adult view of the own executive functions (EF), or self-regulation, in the daily environment. It consists of 9 clinical scales: inhibit (the ability to control impulses; ability to stop one's own behavior at the appropriate time), shift (the ability to move from one situation, activity, or aspect of a problem to another, as the circumstances demand), emotional control (to modulate mood appropriately), self-monitor (to attend to your own behavior in a social context), initiate (to begin a task or activity), working memory (to hold information in mind for the purpose of completing a task), plan/organize (to anticipate future events), task monitor (to check work and assess

one's performance) and organization of materials (to keep workspaces and materials in a orderly manner). It also contains 3 validity scales: negativity, infrequency, inconsistency. These clinical scales form two indices: the Behavioral Regulation Index (BRI; first four scales) which represents the ability to maintain appropriate regulatory control of behavior and emotional responses, and the Metacognition Index (MI; remaining five scales summarized) which represents the ability to cognitively manage attention and problem solving.

The Five Factor Personality Inventory (FFPI) is a 100-item inventory which assesses the Big Five dimensional model of personality (Jolijn Hendriks et al., 2003; Rodríguez-Fornells, Lorenzo-Seva, & Andrés-Pueyo, 2001). It consists of five higher-order personality dimensions assessing extraversion (e.g. being assertive), agreeableness (e.g. being cooperative and tolerant), conscientiousness (e.g. being careful, responsible), emotional stability (e.g. anxiety, depression) and autonomy (e.g. the tendency to make independent decisions).

These two psychometric measures (BRIEF-A and FFPI) made up the self- and hetero- informing questionnaires.

Clinical severity measures. The *Global Assessment of Functioning* (GAF) (APA, 2000) is a numeric scale (0 through 100) in which the clinician rates their impression about social, occupational and psychological functioning.

The *Clinical Global Impression-BPD* (CGI-BPD) (Perez et al., 2007) assesses the degree of severity in BPD patients. It contains 10 items that score the nine relevant psychopathological domains of BPD, as well as an additional global score.

The DIB-R (Barrachina et al., 2004) is a semi-structured interview used in the assessment of core symptoms of BPD and is divided into 4 areas: affect regulation, cognitive disturbance, impulsive behavior and interpersonal relationships. The assessment is focused on the last two years and its score ranges between 0 and 10, with 6 being the cut-off for diagnosing BPD.

Medication load. We computed a composite measure of total medication load used previously in psychiatric samples (Vederman et al., 2012) (see supplementary material in the appendix for details).

11.2.4. Data analysis

Demographical, clinical and psychometric data were computed and for psychometric the ones, direct scores were converted to T scores which were considered in the subsequent analysis. Differences between variables were evaluated using Pearson's Chi-square test (χ^2) for the categorical variables and a *t*-test (paired or independent) to compare mean values.

First, we studied the psychometric differences between informants (self- *vs.* relatives) using a pairwise *t*-test for each BRIEF-A clinical scale and FFPI dimension.

Second, we tested the differences between groups in self-reported information performing an independent *t*-test analysis (BPD versus healthy control participants) on BRIEF-A and FFPI; complementarily, we computed the frequency in which BPD self-reports were beyond the 65 T-score (i.e. mean plus one standard deviation in a T distribution) in each BRIEF-A scale.

Third, we performed a repeated-measures ANCOVA (rmANCOVA) introducing the psychometric profiles of the BRIEF-scales (inhibit, shift, emotional control, self-

monitor, initiate, working memory, plan/organize, task monitor, organization of materials) with Informant (oneself versus relatives) as a within-subject factor and the Group (BPD patients and healthy comparison participants) as a between-subject factor. If the Mauchly tests showed a violation of the sphericity assumption, Greenhouse-Geisser corrections were considered. The Medication load score was included as a covariate in all analysis to control for medication prescription variability.

In accordance with our hypothesis, we focused this rmANCOVA profile analysis on three basic areas:

1. We expected a BRIEF-scales x Group interaction to show differences in the overall profile of EF between groups, independent of the informant (auto or hetero).

2. If a metacognitive deficit existed in BPD participants, we expected a Group x Informant interaction effect in the BRIEF-scales factor. This interaction would reflect that while no differences exist in the controls between self- and hetero- evaluations, a clear difference exists in BPD patients and is independent of BRIEF scales. Conversely, if the deficit is not consistent across the BRIEF-A profile and is only present in some subscales, a BRIEF-scales x Group x Informant interaction should be obtained

3. The same rmANCOVA analysis was carried out with long-term FFPI dimensions (extraversion, agreeableness, conscientiousness, emotional stability, autonomy).

Finally, a bivariate Pearson correlation analysis was carried out to analyze the relationship between BRIEF-A overall indexes (BRI and MI), considering self- minus hetero- scores, and BPD severity measures (only p-values under 0.01 was reported).

11.3. Results

Clinical and demographical data. Clinical, demographical, and social characteristics collected from participants and their relatives are summarized in the Table 1.

Self-assessment on executive functions and personality. Self-reported mean T-scores on BRIEF-A clinical scales and FFPI dimensions are depicted in Table 2. The results suggest that firstly, the BPD patients showed a lower self-view of their own daily EF and self-regulation capabilities (i.e. higher scores in all BRIEF-A clinical scales) and secondly, the BPD patients scored themselves as less extraverted, agreeable, conscientious, emotionally stable and autonomous than the control participants (i.e. lower mean scores in FFPI personality dimensions).

Accordingly, the BPD participants also exceeded the 65 T-score at a higher percentage (range: 33.3-94.6, mean: 72.5, SD: 17.7) than the comparison group (range: 8.3-11.1, mean: 4.3, SD: 2.8) in all BRIEF-A clinical scales (see S1 for a detailed analysis). Hence, this supports the previous result of lower self-evaluation of EF in the BPD patients, compared with healthy participants.

Self- versus Informant-assessment differences. As can be seen in Table 2, the pairwise t-test analysis revealed differences between self and hetero response information on all scales of the BRIEF-A measure in the BPD group and only in self-monitoring scales in the comparison group. Therefore BPD patients judged themselves as less able than that of the evaluation performed on them by their relatives. In contrast, BPD patients showed similar scores to their informants in four of the five personality dimensions, with Emotional Stability being the only significant dimension in which BPD patients reported themselves as less stable. Interestingly, the control group showed

no significant differences in personality for own vs. other's evaluation, except for agreeableness and conscientiousness.

Profile analysis. The profile analysis is shown in Figure 1 (see also table ST2). In accordance with our hypothesis, we found a significant interactive effect between BRIEF-scales and Group (F=3.07, df=4.37, p=0.014) and FFPI-dimensions x Group (F=10.39, df=4, p<0.001). As expected these simply showed that overall both BRIEF-A and FFPI profiles were different depending on the psychopathological condition (see Figure 1).

In addition, a significant interaction of Group x Informant (F=23.72, df=1, p=<0.001) was encountered in the BRIEF-A analysis. This interaction reflects that while no differences existed between self- versus hetero- evaluations in the control group (see Figure 1), BPD patients always scored themselves lower when compared to those of their relatives. This effect was consistent across the whole BRIEF-A profile (the interaction between BRIEF-scales x Group x Informant was not significant, F=.47, df=6.61, p=0.179).

In the corresponding analysis for the FFPI, a marginal but significant interaction effect of Group x Informant (F=4.21, df=1, p=0.044) was observed, suggesting that self- and hetero- information was different in several FFPI-dimensions (the interaction between FFPI-dimensions x Group x Informant was also significant, F=3.59, df=4, p=0.007). Interestingly, healthy participants did not agree with their relatives in two dimensions (agreeableness and consciousness) while BPD participants differed only in one evaluation (emotional stability) (see Table 2). The medication load as a covariate was not related with between-subjects differences and interactive effects previously reported in both analyses (see table S2 in the appendix).

Table 2. Descriptive statistics of psychometric measures divided into information source and group [a]

Variable	**BPD** (n=72)					**CONTROL** (n=72)					Self-BPD vs. Self-Informant
	Self		Informant		Self vs. Informant	Self		Informant		Self vs. Informant	
	Mean	SD	Mean	SD	t-test	Mean	SD	Mean	SD	t-test	t-test
BRIEF											
Inhibit	69.75	11.85	61.15	9.39	5.45 [d]	45.32	7.11	46.04	6.06	-0.74	10.61 [d]
Shift	75.98	10.05	67.18	8.32	5.22 [d]	50.01	9.34	50.63	8.83	-0.47	11.35 [d]
Emotional Control	76.35	6.66	66.89	7.69	7.48 [d]	50.45	8.68	50.28	6.76	0.13	14.21 [d]
Self.Monitor	72.15	10.85	63.42	10.19	4.45 [d]	49.33	11.13	46.28	7.48	2.59 [b]	8.80 [d]
Initiate	74.57	12.06	65.09	11.16	5.29 [d]	47.46	8.85	48.31	7.96	-0.78	10.87 [d]
Working Memory	73.46	13.11	60.91	10.77	6.23 [d]	44.68	7.19	45.05	6.41	-0.25	11.55 [d]
Plan/Organize	71.51	9.06	60.96	7.81	7.05 [d]	49.75	6.96	47.52	6.55	1.85	11.41 [d]
Task Monitoring	69.55	10.61	61.72	9.25	4.47 [d]	47.89	8.95	47.97	7.69	-0.06	9.36 [d]
Org. Materials	58.84	11.56	53.48	10.08	3.13 [c]	46.54	8.26	46.66	8.38	-0.11	5.19 [d]
BRI	79.54	8.51	66.87	7.77	10.01 [d]	50.21	9.04	48.31	6.47	1.76	14.16 [d]
MI	72.68	10.81	61.39	8.35	7.85 [d]	47.17	7.36	46.71	6.68	0.43	11.71 [d]
FFPI											
Extraverersion	43.16	11.30	44.01	10.79	-0.42	53.27	8.12	54.36	8.77	-1.09	-4.35 [d]
Agreeableness	45.58	11.46	40.63	13.95	1.72	54.94	7.02	50.63	9.54	2.91 [c]	-4.17 [d]
Conscientiousness	42.01	10.62	41.25	11.93	0.33	55.83	8.24	59.01	8.28	-2.96 [c]	-6.17 [d]
Emotional Stability	33.51	8.99	39.27	10.31	-2.73 [b]	56.58	7.01	55.97	6.91	0.53	-12.14 [d]
Autonomy	45.38	12.12	46.41	10.97	-0.38	50.16	7.54	48.94	7.78	0.81	-2.01 [b]

[a] The data depict mean T scores for the BRIEF-A clinical scales and overall indexes, Behavioral Rating Index (BRI) and Metacognition Index (MI), as well as for the FFPI personality dimensions. The Student's *t*-test is presented for self- and informant-reports comparisons for each group as well as for self-reports comparisons. The data shows that the differences between informants were statistically significant for BRIEF-A only in the BPD group but not in the Control one and, for the FFPI, this difference is centered in FFPI-Emotional Stability scale for the BPD group and in Agreeableness dimension for the Comparison group. Concerning self-reports the *t*-test analysis shows statistical differences between groups both for BRIEF-A and FFPI. [b] $p<0.05$; [c] $p<0.01$; [d] $p<0.001$

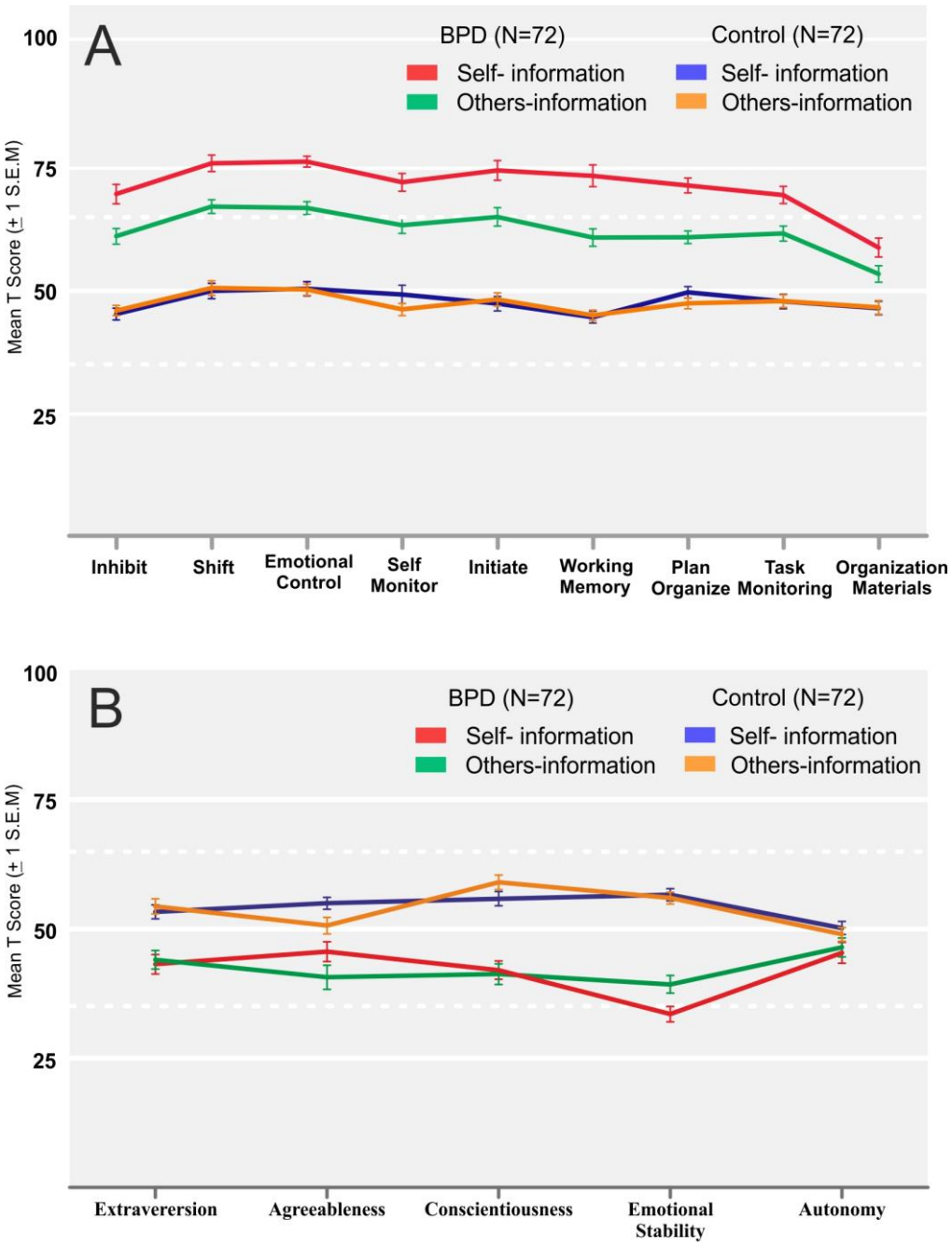

Figure 1. BRIEF-A and FFPI profiles for BPD and Control groups [a]

[a] The figure shows T mean scores of the information provided by each participant (self-information) and by their corresponding informants (others-information). The dotted line shows the ± 1 SD of the mean (65 and 35 T-scores), indicating the limits of the normal T distribution. Panel A shows the data from BRIEF-A of BPD patients and control participants, and corresponding to their informants. In the panel B is shown the data obtained in the FFPI.

Relationship between BRIEF-A and clinical severity measures. Concerning the BRIEF-A overall indexes, we found that the difference between self- and informant-reports (i.e. metacognitive accuracy) on BRI was associated with the DIB-R cognitive area ($r=0.47$, $p<0.01$). Thus, the poorer metacognitive accuracy in BRI index (i.e. the ability to maintain appropriate regulatory control of behavior and emotional responses) was associated with a higher presence of strange, suspicious and paranoid thoughts. Differences in MI was associated with the CGI Paranoid dimension ($r=0.45$, $p=0.01$), suggesting that the poorer metacognitive accuracy in the MI index (i.e. the ability to cognitively manage attention and problem solving) was associated with most paranoid symptoms (see Figure 2).

We found no significant correlations with other clinical or functional measures (e.g. GAF).

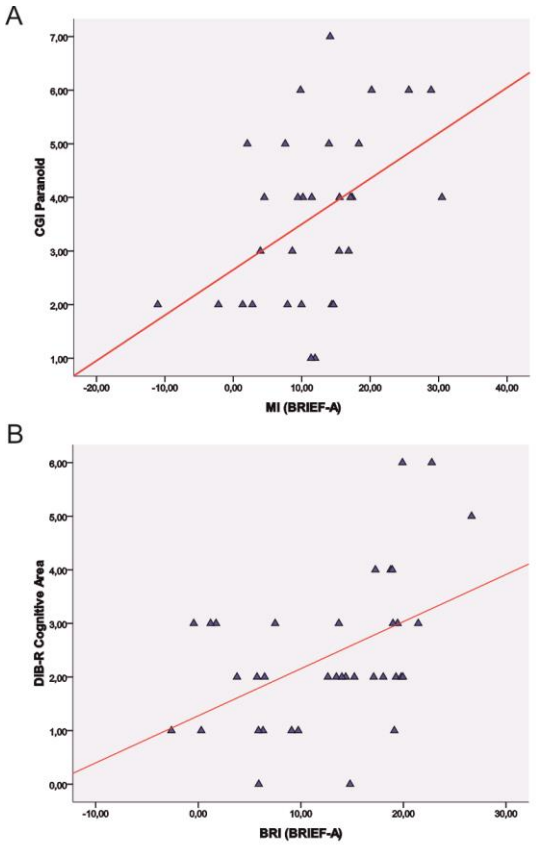

Figure 2. Correlation between BRIEF-A overall indexes (BRI and MI) and clinical measures

[a] The BRIEF-A overall indexes were computed based on the difference between self- and informant-reports. In panel A, scatterplot depicts the correlation between BRIEF-A MI index and CGI-paranoid severity dimension ($R^2=0.206$). In panel B scatterplot depicts the correlation between BRIEF-A BRI index and DIB-R cognitive area ($R^2=0.221$).

11.4. Discussion

The present study investigated for the first time the metacognitive abilities of a BPD sample (and a matched control group) in relation to their self-regulatory and cognitive control capacities. We analyzed these processes in daily-life activities by means of a comparison between self-image evaluations vs. external perception by their close relatives. Importantly, we identified a robust but isolated negative bias of BPD patients in the metacognitive evaluation of their self-regulatory capacity, which do not generalize to other self-image domains (long-lasting personality traits). In addition, these are the first empirical data on executive functions (EF) evaluated using the BRIEF-A in a well characterized BPD sample.

Importantly, metacognitive deficits may involve an inability to monitor (or be aware of) one's own symptoms and a diminished capacity to accurately self-appraise behaviors (Schmitz, Rowley, Kawahara, & Johnson, 2006). This (in)capacity has been linked with PFC areas (mainly ventromedial, rostrolateral, dorsolateral and cingulated regions) and, usually, patients with damage in these brain regions show a discrepancy between their self-perception and the current level of functioning (they underestimate their functional limitations) (Schmitz & Johnson, 2007). Interestingly, in the present study we found that BPD participants overestimated their daily functional limitations. It was confirmed by a poorer self-appraisal (i.e. profile analysis) than that of their relatives in the BRIEF-A assessment. Thus, while healthy participants properly monitor their daily executive functioning, BPD patients show a lesser ability to do so. Most importantly, this metacognitive deficit was selective for cognitive control and self-regulation mechanisms but not for most of the personality dimensions evaluated (FFPI). Indeed, the only personality trait which showed significant differences in accuracy was

emotional stability, thus patients again viewed themselves as less stable than their informants did. This finding is in line with previous results using personality measures (Klonsky et al., 2002). In addition, these results are consistent with recent findings of feedback processing alterations in BPD patients (Vega et al., 2013), which has been associated with self-regulation problems and increased difficulties in adapting their behavior based on previous experiences. This alteration may result from a metacognitive incapacity for monitoring proper cognitive resources in processing relevant external stimuli [see for a review on this topic: (Northoff & Hayes, 2011)].

The present results suggest that metacognitive deficits play a key mediating role between the altered cognitive processes responsible for self-regulation and cognitive control [not always captured by traditional laboratory-based tasks: (Hagenhoff et al., 2013)] and the daily-life consequences in these patients. Thus first, even when these problems were present and were easily observable by their close relatives, BPD patients showed an altered capacity in their monitoring and to a certain extent overestimated their difficulties. One possibility is that this negative self-image bias on their own functioning might affect self-efficacy (Akama, 2006), which is in accordance with previous studies showing reduced self-confidence in these patients (Koenigsberg et al., 2010). People who are low in self-efficacy are easily discouraged by challenges and failures, tend not to apply appropriate self-regulatory goals and also experience frequent emotional disturbances (Clark & Beck, 2010; Nelson & Narens, 1994) just as is often observed in BPD patients (Skodol et al., 2002). Indeed they often have maladaptive behaviors such as non suicidal self-injury acts for self-regulating their stress emotions (Glenn & Klonsky, 2009). Second and importantly, poor metacognitive skills not only involve difficulties in the monitoring of suitable strategies for different tasks but also in the conditions under which these strategies might be used and in the knowledge of the

extent to which these strategies are effective (Flavell, 1979; Pintrich, 2002). Therefore, in BPD patients it seems plausible that these impairments result in difficulties in their capacity to correctly plan and learn in a flexible manner, as well as in their ability to voluntarily re-appraise aversive stimulus [see for example, (Schuermann, Kathmann, Stiglmayr, Renneberg, & Endrass, 2011; Schulze et al., 2011)]. Finally, the notion of a metacognitive deficit in these patients is reinforced by the greater effectiveness of psychological treatments rather than psychopharmacological ones (Stoffers et al., 2012). Thus, some of these treatments are directed to improving BPD patients' clinical status by means of enhancing in the monitoring of daily-life activities. For instance, mindfulness training, an active component of dialectical behavioral therapy (Linehan, 1993) promotes the awareness of all emotional and cognitive events as they occur in the present, promoting a shift in mental processes rather than a direct change of the mental contents or behaviors. (Chiesa, Serretti, & Jakobsen, 2013).

Importantly we also observed a clear relationship between metacognitive deficits (considering both overall indexes of the BRIEF-A) and clinical status in the BPD group. Low metacognitive accuracy (higher self- vs. informant- discrepancy) in BRI and MI indexes was associated with a higher presence of strange, suspicious and paranoid thoughts (but not psychotic, showing higher scores in DIB-R cognitive area and in CGI-paranoid scale). Importantly, this result suggests that metacognitive deficits observed in BPD participants could be, at least partially, related to biases in social feedback processing [a core aspect of the disorder; see, (Roepke, Vater, Preißler, Heekeren, & Dziobek, 2012)] and with the integration of this kind of information for appropriated self-regulation, monitoring and cognitive control [see in the introduction: (Bateman & Fonagy, 2004)].

Previous neuropsychological studies using traditional tasks, have not agreed on EF alterations in BPD patients (Hagenhoff et al., 2013). Here, using for the first time a more ecological measure, the BRIEF-A, we found alterations in a wide range (all scales) of EF involved in 'real-world' daily activities which in turn fits well with self-regulation and cognitive control problems in these patients (Skodol et al., 2002).

The fact that all patients were females, although ecologically valid, could affect the generalization of these results as being a study limitation. Future studies need to include EF performance-based tasks in combination with self-reported inventories in order to evaluate the effectiveness of BPD-treatment. Furthermore, the presence of metacognitive deficits in other psychiatric samples needs to be considered using the multi-informant approach.

In summary, the present study provides consistent evidence of a deficit in metacognitive monitoring of self-regulation processes involved in daily functioning of a BPD sample and constitutes the first BRIEF-A data gathered on these patients.

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Chapter IV:
General discussion and conclusions

12. General discussion

A better understanding of BPD is a fundamental necessity in clinical neuroscience and psychiatry. One of the most prominent characteristics in these patients is the presence of NSSI behaviours, having said that, the relationship between these two clinical entities (NSSI and BPD) has remained poorly studied. In this dissertation we addressed these issues. In the previous chapters, four experiments employing behavioural, psychometric and neuropshysiological techniques have explored the nature of BPD and NSSI behaviours. A discussion concerning each of the studies is included in the corresponding chapter. Here, in the present section, a general discussion about the experiments will be offered as well as some comments on the limitations and suggestions on possible future lines of research.

Reward processing in BPD patients and its relationship with NSSI behaviours.

The idea of a dysfunctional reward system in BPD has received growing theoretical interest in recent years (Bandelow, Schmahl, Falkai, & Wedekind, 2010). Despite this, research that has directly tested the reward processing in BPD patients has been scarce (Enzi et al., 2011; Schuermann, Kathmann, Stiglmayr, Renneberg, & Endrass, 2011; Völlm et al., 2007). Furthermore, possible alterations in the learning process, which require the ability to predict rewards, and its relationship with NSSI behaviours is an issue that has not previously been studied.

In this thesis we investigated the reward processing in BPD patients. To that end, thirty-six participants (eighteen borderline patients and eighteen healthy individuals) took part in an ERP experiment. On the other hand, sixty subjects (forty borderline patients and twenty healthy participants) took part in a fMRI study in which we divided

BPD participants in function of the presence of NSSI behaviours. In both studies a similar gambling task was used to evaluate gain and loss feedback processing.

As we predicted, BPD patients showed alterations in reward processing. This finding suggests an impaired mesolimbic dopaminergic system in these patients involving, among other brain regions, the ACC (experiment 1) and the OFC (experiment 2). Concretely, we found that BPD patients showed alterations in two reward-related ERP components (the FRN amplitude and theta oscillatory activity). On the other hand, interestingly, we found that BPD patients with NSSI behaviours presented an enhanced activation in the bilateral OFC (in comparison to both healthy and borderline subjects without NSSI behaviours). This sub-group of patients also showed diminished functional connectivity between the left OFC and the right parahippocampal gyrus when compared to healthy controls.

Cognitive control *in BPD patients and its relationship with NSSI behaviours.* In this section we conducted two experiments which investigated different processes associated with cognitive control. To that end, fifty-one participants (thirty-four borderline patients and seventeen healthy individuals) took part in an ERP experiment whereas, on the other hand, seventy-two subjects (thirty-six borderline patients and thirty-six healthy participants) took part in a psychometric study. In the first study we evaluated the error processing using an Eriksen Flanker task (Eriksen & Eriksen, 1974). In the second one, the metacognitive capacity was evaluated using a multi-informant assessment methodology by means of the BRIEF-A inventory.

We expected an impaired cognitive control capacity (error processing and metacognition) in BPD patients, in particular in those borderline patients who presented self-harming behaviours. We found consistent evidence of a deficit in metacognitive

monitoring of self-regulation processes involved in the daily functioning of BPD patients, in line with our predictions. However, contrary to our initial hypothesis and previous studies (de Bruijn et al., 2006; Ruchsow, Walter, Buchheim, Martius, Spitzer, et al., 2006), we found that error detection and monitoring capacity is preserved in BPD patients (independent of the presence of NSSI behaviours), as the analysis of ERP-components associated with errors showed (Error-Related Negativity, Pe and theta power increase).

Implications and future lines of research. All these findings allow us a better understanding of the BPD phenomenology and may have important implications in the treatment of these patients. In addition, some of the results obtained are unexpected and novel and may lead to further lines of research in the future.

First, we found that BPD patients present alterations in the processing of negative feedback. This is an important finding because, independent of possible clinical depression, it evidences a dysfunctional reward processing system in BPD patients (study 1). In particular, this impairment demonstrates a tendency to experience negative expectations which lead these patients towards an incapacity for adjusting their behaviours and making predictions according to the history of previous outcomes, resulting in difficulties in their day to day functioning and self-regulation.

In line with this, interestingly, we also identified a complementary negative bias in BPD patients in the metacognitive evaluation of their self-regulatory capacity, which do not generalize to other self-image domains (long-lasting personality traits). Metacognition refers to higher-order self-reflective cognitive processes that may be used for regulating information processing and for evaluating one's cognition and behaviour (Metcalfe & Shimamura, 1996; Yeung & Summerfield, 2012). Thus, the

present results suggest that BPD patients show deficits in their ability to monitor (or be aware of) their own symptoms as well as a diminished capacity to accurately self-appraise behaviours. As a possible consequence of this impairment, these patients might suffer a pervasive self-efficacy or self-confidence distortion which, in turn, results in a tendency to apply inappropriate self-regulatory goals and also experience frequent emotional disturbances. Poor metacognitive skills not only involve difficulties in the monitoring of suitable strategies for different tasks, but also in the conditions under which these strategies might be used and the knowledge of the extent to which these strategies are effective. Here it is noteworthy to mention that in this dissertation we evaluated metacognition by using an innovative methodology not previously used with BPD subjects. Thus, these results represent an advance in the understanding of how these patients present daily self-regulation disturbances beyond those problems that might be witnessed in the 'laboratory' task performance (Burgess, Alderman, Evans, Emslie, & Wilson, 1998).

In addition to metacognition, concerning cognitive control, we also investigated error processing in BPD patients. Interestingly, our results showed that these mechanisms are preserved in BPD patients, contrary to our hypothesis and previous studies (de Bruijn et al., 2006; Ruchsow, Walter, Buchheim, Martius, Gro, et al., 2006). Therefore, BPD patients are able to detect, monitor and inhibit erroneous behaviours in an efficient way.

A second aim of the present dissertation was to address an important question that has been scarcely investigated in BPD patients: that of NSSI behaviours.

Interestingly, we found that NSSI behaviours in BPD patients cannot be explained by a dysfunction in error monitoring. This is very relevant in the understanding of this complex phenomenon, and suggests that these behaviours respond to a variety of

functions. Thus, not all self-injurers engaged in these behaviours impulsively or in an "out of control" manner, however, they might have spent some time thinking about NSSI before engaging in it as an emotional self-regulation strategy (Chapman, Gratz, & Brown, 2006; Klonsky, 2007). Therefore, reiterative self-harming is not associated with a systematic failure in internal error-signals processing (ERN, Pe), but with reinforced contingencies [*e.g.* feel alive, stop arguing, (Nock, 2010)]. In this line, we found a clear dissociation in reward processing when comparing SI-BPD to NI-BPD patients in the fMRI study. Those BPD patients with NSSI behaviours presented an enhanced activation in the bilateral OFC (see study 3). This result supports a role of learning in the generation and maintenance of NSSI behaviours and suggests the OFC plays an essential role. In particular, this enhanced activity might point to an impairment in inhibitory control in the emotion regulation of this sub-group of BPD patients (Ruocco, Amirthavasagam, Choi-Kain, & McMain, 2013). Interestingly this brain region is involved in higher-order cognitive functions (Narender Ramnani & Owen, 2004) such as metacognition (Metcalfe & Shimamura, 1994). Furthermore, the OFC has also been related with the processing of secondary reinforcers (such as money or social judgments) (Sescousse, Caldú, Segura, & Dreher, 2013; Sescousse, Redouté, & Dreher, 2010), and plays an important role in the generation of reward expectations and predictions (Ramnani & Miall, 2003; Rushworth, Behrens, Rudebeck, & Walton, 2007), thus guiding individuals' selection of advantageous over disadvantageous behaviour based on previous experience (Kringelbach & Rolls, 2004).

Taken together, these results concerning NSSI behaviours are congruent with Linehan's biosocial theory (Crowell, Beauchaine, & Linehan, 2009), insomuch as NSSI behaviours are maladaptive attempts to self-regulate negative emotional states which, in turn, are positively and/or negatively reinforced by their outcomes. Interestingly, these

findings propose NSSI behaviours as being a possible behavioural phenotype of reward-related alterations in BPD patients. This innovative approach to the NSSI phenomena takes into account biological evidence from two different BPD sub-groups (in function of the presence of NSSI behaviours), congruently to their clinical heterogeneity (Skodol et al., 2002).

It is important to notice that because of their preserved error-monitoring system, the learning of alternative self-regulating strategies (more adaptive than NSSI) is possible in most BPD patients who undergo psychological treatment, showing that they are able to process the internal error signals adequately, in contrast to the external feedback (King-Casas et al., 2008). Furthermore the present findings open the door to possible individualized clinical treatment for different BPD patients; therefore ever more personalized approaches could be considered in function, for example, of the presence of NSSI behaviours.

Future research must address how alterations in reward processing and metacognition in BPD patients may improve after a specific psychological intervention (e.g. dialectic behaviour therapy). When considering these two high-cognitive functions, it seems reasonable to expect that self-regulation training might result in an enhanced capacity for establishing appropriate predictions and expectations (based on previous experiences), as well as in the metacognitive ability of a subject´s cognitive control. For instance, mindfulness training, an active component of dialectical behavioural therapy, promotes the awareness of all emotional and cognitive events as they occur in the present moment (Larson, Steffen, & Primosch, 2013).

In the present thesis we observed a clear differentiation between BPD patients in function of the presence or not of NSSI behaviours, suggesting a relationship between NSSI and OFC activity. This finding is in accordance with structural neuroimaging data

from BPD patients obtained by our group (Salvador et al., in press). Therefore, an early detection of these kinds of behaviours may help to highlight risk groups and to develop preventive interventions in the community. Concretely, these interventions should be focused on OFC functions. For instance, the representation of the reward value of abstract reinforcers (O'Doherty, 2004), the generation of reward expectations and predictions (Ramnani & Miall, 2003; Rushworth et al., 2007) and the selection of advantageous over disadvantageous behaviour based on previous experience (Kringelbach & Rolls, 2004). Currently, we have several, evidence-based interventions for BPD patients (Stoffers et al., 2012) which are able to change some of these aspects but, however, there are no preventive (primary or secondary) interventions, which address NSSI, for non-clinical samples.

Following on from this, additional research is required to study if OFC reward-related alterations are maintained in non-clinical samples with NSSI behaviour or in other clinical groups (different to BPD), thus focusing on NSSI beyond the categorical approach of mental disorders (Nock & Prinstein, 2004). In addition, to establish age cohorts might help to determine whether present findings are age-specific or not.

Once two sub-groups of BPD patients in function of the presence of NSSI behaviour are investigated, the door to the design of more specific treatments is opened. Thus, future studies must address the question of whether all BPD patients need the same intensity of psychological treatment. For example, complex interventions such as Dialectical Behaviour Therapy (Linehan, 1987) or Mentalization Based Therapy (Bateman & Fonagy, 2004), which are long and intensive treatments, would be suggested as the first treatment option for those BPD patients with NSSI, while other treatments such as the System Training for Emotional Stability and Problem Solving

(Blum, Pfohl, John, Monahan, & Black, 2002) would be offered to those patients without NSSI.

The use of social paradigms must help to complement these findings in favour of external signals processing in BPD patients (Dziobek et al., 2011). In particular, in those patients who present NSSI because, commonly, these behaviours appear more in social situations.

The lack of integration between the psychometric data and fMRI or ERP findings, which can be considered as a limitation of the present thesis, is a clear target for future studies. In addition, the tranversal desing used in this thesis is also a limitation.

Finally, given the discovery of preserved error processing mechanisms in BPD patients, future studies should replicate this result using an error processing tasks (such as the Ericksen Flanker task) under an emotional induction. For example, the combination of using emotion-inducing slides and classical trials of the Ericksen Flanker task would help us to understand the relationship between the processing of errors and emotions. This kind of task seems a most ecological option in the study of BPD.

13. Conclusions

The main conclusions of the thesis can be summarized as follows:

i. BPD patients present alterations in the reward system

ii. BPD patients show a decrease in the amplitude of the Feedback Related Negativity ERP-component and of the power of theta activity. These alterations suggest a deficit in negative feedback processing which lead to deficits in learning

and decision making due to an impaired capacity to elicit correct expectations and predictions.

iii. Those BPD patients with NSSI (SI-BPD) present an enhanced activation in the bilateral OFC when compared to both healthy and NI-BPD participants. This sub-group of BPD patients shows also a diminished functional connectivity between the left OFC and the right parahippocampal gyrus when compared to healthy controls.

iv. Due to the enhanced activity in the OFC, SI-BPD patients might present impairment in reward-guiding behaviors and reward-based predictions in comparison to NI-BPD patients.

v. Error monitoring mechanisms are preserved in BPD and, even in those BPD patients with NSSI behaviours.

vi. BPD patients present deficits in metacognitive monitoring on daily self-regulation and cognitive control processes. These problems are attuned with most BPD main symptoms.

References: introduction and general discussion

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Appendix

Appendix I:

Journal Publication:

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Negative reward expectations in Borderline Personality Disorder patients: Neurophysiological evidence

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ABSTRACT

Borderline Personality Disorder (BPD) patients present profound disturbances in affect regulation and impulse control which could reflect a dysfunction in reward-related processes. The current study investigated these processes in a sample of 18 BPD patients and 18 matched healthy controls, using an event-related brain potentials methodology. Results revealed a reduction in the amplitude of the Feedback-Related Negativity of BPD patients, which is a neurophysiological index of the impact of negative feedback in reward-related tasks. This reduction, in the effect of negative feedback in BPD patients, was accompanied by a different behavioral pattern of risk choice compared to healthy participants. These findings confirm a dysfunctional reward system in BDP patients, which might compromise their capacity to build positive expectations of future rewards and decision making.

1. Introduction

Borderline Personality Disorder (BPD) is a complex and serious mental disorder with a characteristic pervasive pattern of instability on affect regulation, impulse control, interpersonal relationships and self-image, and severe functional impairment (Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004). Although it seems to be a heterogeneous and less stable diagnosis (Zanarini, Frankenburg, Reich, & Fitzmaurice, 2010), emotion dysregulation is the most permanent and frequent criterion (Carpenter & Trull, 2013; Glenn & Klonsky, 2009). Some influential accounts on the etiology of BPD propose that patients present an impairment in the processing of critical information in the adaptation of behavior to environmental contingencies (e.g., rewards and punishments associated with their actions) which would compromise their emotional self-regulation (Crowell, Beauchaine, & Linehan, 2009). Nevertheless, studies on the processing of rewarding outcomes as well the expectations of receiving a reward have been scarce in these patients.

Emotional reactivity and cognitive control have been proposed as two features of the BPD emotional difficulties and, additionally, have been related to their attachment style which plays a central role in the development of the disorder (Agrawal, Gunderson, Holmes, & Lyons-Ruth, 2004; Minzenberg, Poole, & Vinogradov, 2008; Steele & Siever, 2010). Rodent models and human neuroimaging have related the attachment system with the reward network due to a shared neural circuit which links a neuropeptide-sensitive mechanism (oxitocin/vasopressin), within the anterior hypothalamus, to the ventral tegmental area (VTA) and nucleus accumbens (see for a review Insel & Young, 2001). In addition, from a gene-environment perspective, the dopamine DRD4 polymorphism in children has been related to disorganized attachment patterns with parents (Lakatos et al., 2000). The reward system is related to a variety of motivated behaviors and cognitive processes, such as reinforcement learning, novelty processing, action monitoring, decision making or addiction (Camara, Rodriguez-Fornells, Ye, & Münte, 2009). Therefore, the interaction between these two systems (reward and attachment) may be especially important for mediating the rewarding properties of social interaction as salient-motivating cue, and for affect and stress regulation (Strathearn &

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Appendix II:

Supplementary material: Chapter II, section 9

Alterations in the reward system differentiate Borderline Personality Disorder patients in function of the presence of non-suicidal self-injury behaviors

Supplementary Table 1. Complementary clinical data for SI-BPD and NI-BPD groups

	SI-BPD	NI-BD
SCID-I (current)		
Any anxiety disorder [a]	6 (30)	
PTSD	0	2 (10)
Eating Disorder	6 (30)	4 (20)
Drug abuse[b]	7 (35)	3 (15)
Others[c]	5 (25)	3 (15)
SCID-I (past)		
Mood disorder	8 (40)	9 (45)
Any anxiety disorder [a]	3 (15)	3 (15)
PTSD	1 (5)	2 (10)
Eating Disorder	3 (15)	3 (15)
Drug dependence	8 (40)	3 (15)
SCID-II		
Avoidant	3 (15)	1 (5)
Dependent	5 (25)	5 (25)
Obsessive-compulsive	1 (5)	0
Paranoid	5 (25)	1 (5)
Schizotypal	2 (10)	0
Antisocial	6 (30)	1 (5)

Note. Percentages (%) of current and lifetime disorders as well as personality disorders.
PTSD = Posttraumatic Stress Disorder
[a] Anxiety disorders except Posttraumatic Stress Disorder
[b] Excluding two months before the scanning
[c] Other mental disorders such as adaptive disorders

Supplementary Table 2. NSSI methods

	SI-BPD
NSSI	
cutting	155.68 (208.08)
biting	68.79 (154.99)
burning	3.47 (6.59)
carving	54.94 (156.54)
needle-sticking	55 (156.94)
hair pulling	61.05 (156.37)
scratching	17.36 (32.91)
banging	102.47 (178.71)
wound picking	65.68 (156.11)
rubbing	38.89 (100.44)
pinching	6.05 (22.88)
chemicals	28.21 (114.35)

Note. Mean scores (+ S.D) of NSSI methods assess with the ISAS.

Appendix III:

Supplementary material: Chapter III, section 10

Preserved error-monitoring in Borderline Personality Disorder patients with and without non-suicidal self-injury behaviors.

SUPPLEMENTAL ANALYSIS

Behavioral Results. Reaction Times and percentage of responses are shown in the Table S1.

Table S1. Flanker Task Behavioral results

	Controls (N=17)		SI-BPD (N=17)		NI-BPD (N=17)		Group effect	
	M	SD	M	SD	M	SD	*F* (2,48)	*P* value
RT (*ms.)*								
Correct	450.73	63.19	483.24	65.63	468.99	50.43	1.249	.296
Error	319.60	39.99	330.47	48.09	361.00	64.42	2.914	.064
Compatible Correct	433.80	60.39	464.46	69.57	456.23	53.88	1.127	.332
Incompatible Correct	462.33	65.77	496.41	64.04	478.16	49.16	1.368	.264
Post-error-slowing	41.03	25.53	23.51	36.09	31.54	34.48	1.248	.296
SSRT	297.09	58.79	328.50	66.98	316.48	50.67	1.219	.305
Response (%)								
Total Correct	91.61	6.03	88.53	9.09	468.99	50.43	.932	.401
Total Error	4.14	4.31	4.12	2.52	361.00	64.42	.665	.519
Compatible Correct	93.99	4.23	91.96	7.26	456.23	53.88	.577	.565
Incompatible Correct	90.43	7.67	86.38	10.50	478.16	49.16	1.167	.320
Inhibited	38.17	22.00	37.27	14.58	38.79	15.01	.032	.969
Non-Inhibited	61.80	21.98	62.71	14.55	61.13	15.08	.035	.966
Corrected errors	56.13	36.43	64.37	30.06	57.13	30.29	.328	.722
Excluded trials	16.62	9.52	21.42	20.46	17.44	16.17	.437	.649

Means of Reaction times (RT; for each condition, post-error-slowing and SSRT) and of percentage of Responses, in the performance of the Flanker Task. Data are depict for each group, and can be observer the corresponding ANOVA with associated *P* values.

Filtered Response-locked ERP data. To discard differences in the response-locked activity between the Control and two BPD groups, we filtered the ERP response-locked data to differentiate between the activity associated to the delta (1-3 Hz) and theta frequencies (3-9 Hz).

In addition, we firstly entered the theta-ERN mean amplitude (measured between 55-75 ms) and theta-Pe mean amplitude (measured between 170-220ms) in the same rmANOVA as the not filtered analysis. The increase in the theta-ERN activity after errors was confirmed by the significant main effect of Response [$F(1,48) = 76.001$, $p < .001$]. Importantly, no main effect of Group [$F(2,48) = .847$, $p = .435$] nor interaction

Response x Group [$F(2,48) = .508$, $p = .605$] were found, showing no theta-ERN amplitude differences between groups. On the other hand, no differences between correct and error trials were found in the theta-Pe time-window [main effect of Response: $F(1,48) = .689$, $p = .411$], as well as no significant main effect of Group [$F(2,48) = .696$, $p = .504$] nor interaction Response x Group effect [$F(2,48) = .149$, $p = .862$] were encountered.

Secondly, we entered the delta-ERN mean (measured between 60-90 ms) and delta-Pe (mean amplitude measured between 240-290ms) amplitudes in the subsequent rmANOVA. No statistical main effect of Response were found between the correct and error trials for delta-ERN [$F(1,48) = .012$, $p = .912$], and no group differences were found as there were no main effect of Group [$F(2,48) = .003$, $p = .997$] nor Response x Group interaction [$F(2,48) = .132$, $p = .876$]. Error trials showed significant main effect of condition in the delta-Pe [$F(1,48) = 106.550$, $p < .001$]. Importantly, no delta-Pe differences were found between groups [main effect of group: $F(2,48) = .674$, $p = .514$; interaction between condition and group: $F(2,48) = .753$, $p = .476$].

Medication load. To study possible effects of medication in the results found we carried out the same analysis introducing the Medication Load as covariate in the rmANCOVA. No significant effects of medications were found in the ERP contrasts, neither the ERN [Main effect of Medication load: $F(1,30) = .369$, $p = .548$; interaction Response x Medication load: $F(1,30) = .000$, $p = 1.000$], nor for the Pe [Main effect of Medication load: $F(1,30) = .550$, $p = .464$; interaction Response x Medication load: $F(1,30) = .254$, $p = .618$]. Similarly, no significant effects of medication were found for the theta time Frequency analysis [Main effect of Medication load: $F(1,30) = .736$, $p = .398$; interaction Response x Medication load: $F(1,30) = .085$, $p = .772$]. Finally, no

significant effects of medication were found in any filtered ERP analysis, for the theta-ERN [Main effect of Medication load: $F(1,30) = .007$, $p = .932$; interaction Response x Medication load: $F(1,30) = .136$, $p = .715$], for the theta-Pe [Main effect of Medication load: $F(1,30) = .481$, $p = .493$; interaction Response x Medication load: $F(1,30) = 2.680$, $p = .112$], for the delta-ERN [Main effect of Medication load: $F(1,30) = 1.050$, $p = .314$; interaction Response x Medication load: $F(1,30) = .058$, $p = .811$], and for the delta-Pe [Main effect of Medication load: $F(1,30) = 1.177$, $p = .287$; interaction Response x Medication load: $F(1,30) = .016$, $p = .901$].

Appendix IV:

Supplementary material: Chapter III, section 11

Deficits in metacognitive monitoring of daily self-regulation processes in Borderline Personality Disorder patients.

Supplemental Information

Supplemental Methods & Materials

Measures. We used a protocol to assess total medication load previously used in psychiatric samples (Vederman et al., 2012). Anti-depressant, anxiolytic, mood stabilizer, and anti-psychotic medications were coded as absent = 0, low = 1, or high = 2 based on previously employed methods to convert each medication to a standardized dose (Almeida et al., 2009; Sackeim, 2001). Anti-psychotics were converted into chlorpromazine dose equivalents (Davis & Chen, 2004). As a result, we obtained a composite measure of total medication load by summing all individual medication codes for each individual medication within categories for each BPD patient.

Data Analysis. Additional repeated-measures ANOVA (rmANOVA) were conducted introducing, the psychometric profile of the BRIEF-scales (inhibit, shift, emotional control, self-monitor, initiate, working memory, plan/organize, task monitor, organization of materials) as within-subject factor, and Group (BPD patients and Comparison subjects) and Relationship (Parent, Partner, Other) as between subjects factors. The same rmANOVA was performed introducing BRIEF-scales (inhibit, shift, emotional control, self-monitor, initiate, working memory, plan/organize, task monitor, organization of materials) as within-subject factor, and Group (BPD patients and Comparison subjects) and Informant-Sex (men, women) as between-subject factor.

If Mauchly tests showed violation of the sphericity assumption, Greenhouse-Geisser corrections were considered. Medication load score was included as a covariate in all analysis to control for medication prescription variability.

Supplemental Results

The BRIEF-A profiles was not affected by informants' variables, as no significant interaction BRIEF-scales x Relationship (F=0.74, df=8.69, p=0.751) was encountered nor interaction BRIEF-scales x Relationship x Group (F=0.93, df=8.69, p=0.499). Otherwise, no significant interaction BRIEF-scales x Informant-sex (F=0.64, df=4.45, p=0.650) was encountered nor interaction BRIEF-scales x Relationship x Group (F=1.29, df=4.45, p=0.269).

Supplemental Tables

Table S1. Percentage of participants who exceeds the 65 T-score in the BRIEF-A clinical scales [a]

	Group		Analysis
	BPD	Comparison	Chi-square
Inhibit	63.9	2.8	30.25
Shift	80.6	2.8	44.81
Emotional Control	94.6	5.4	56.88
Self Monitoring	86.1	11.1	40.53
Initiate	75	5.6	30.08
Working Memory	75	2.8	39.51
Plan/Organize	80.6	2.8	44.81
Task Monitoring	63.9	2.8	30.25
Organization Materials	33.3	2.8	11.35

[a] The data depict the percentage of elevated scores in the BRIEF-A clinical scales, indicated by T-scores of 65 or greater (which are at least 1.5 points above to the mean). Pearson's Chi-square test shows significant differences in all scales (at $p<0.001$) between BPD and Comparison groups.

Table S2. Repeated measures ANCOVA for BRIEF-A and FFPI profiles [a]

Factor	df	*F*	η^2	p
BRIEF-A				
Within-subjects				
BRIEF[b] x Group	4.38	3.01	0.42	0.015
BRIEF x Informant	6.61	2.17	0.31	0.039
Informant x Group	1	23.64	0.26	<0.001
BRIEF x Informant x Group	6.61	1.55	0.02	0.152
Between-subjects				
MedLoad[c]	1	0.64	0.01	0.426
Group	1	110.19	0.61	<0.001
FFPI				
Within-subjects				
FFPI[d] x Group	4	10.39	0.13	<0.001
FFPI x Informant	4	4.23	0.58	0.002
Informant x Group	1	4.21	0.57	0.044
FFPI x Group x Informant	4	3.59	0.49	0.007
Between-subjects				
MedLoad	1	0.25	0.01	0.618
Group	1	76,12	0.52	<0.001

[a] The data depict ANCOVA analysis for BRIEF-A and FFPI profiles

[b] BRIEF = BRIEF-scales

[c] MedLoad = Medication load covariate

[d] FFPI = FFPI-scales

Supplemental References

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Appendix V:

In-press journal publication:

Salvador, R., Vega. D., Pascual, J.C., Canales-Rodriguez, E., Aguilar, S., Anguera, M., Soler, J., Maristany, R., Rodríguez-Fornells, A., Marco-Pallarés, J., Pomarol-Clotet, E. (in press). Converging medial frontal resting state and diffusion based abnormalities in borderline personality disorder. *Biological Psychiatry*

Abstract

Background: The psychological profile of Borderline Personality Disorder (BPD) patients, with impulsivity and emotional dysregulation as core symptoms, has guided the search for abnormalities in specific brain areas such as the hippocampal-amygdala complex and the fronto-medial cortex. So far, though, whole brain imaging studies have delivered highly heterogeneous results involving different brain locations.

Methods: Resting state functional Magnetic Resonance Imaging (MRI) and diffusion MRI was acquired on BPD patients and on an equal number of matched controls (N = 60 for resting and N = 43 for diffusion). While Mean diffusivity (MD) and Fractional Anisotropy (FA) brain images were generated from diffusion data, the Amplitude of Low Frequency Fluctuations (ALFF) and Global Brain Connectivity (GBC) images were used for the first time to evaluate BPD related brain abnormalities from resting functional acquisitions.

Results: Whole brain analyses using a p = 0.05 corrected threshold showed a convergence of BPD alterations in genual and perigenual structures, with frontal white matter FA abnormalities partially encircling clusters of increased MD and GBC values. A cluster of enlarged ALFF (high resting activity) was located in part of the left hippocampus and amygdala. In turn, this cluster showed increased resting functional connectivity with a cluster in the anterior cingulate.

Conclusions: With a multimodal approach, and without using a priori selected regions, we prove that structural and functional abnormality in BPD involves both temporo-limbic and fronto-medial structures, as well as their connectivity, all of them extensively related to behavioral and clinical symptoms in BPD patients.