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Neural Parameters of Therapeutic Change in Interpersonal Psychotherapy for Borderline Personality Disorder: one-year follow up fMRI study.

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To my baby Leo with Love

&

Gratitude.

Table of Content

Neural Parameters of Therapeutic Change in Interpersonal Treatment for Borderline Personality Disorder: one-year follow-up fMRI study.

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Despite better characterization of neural deficits mediating symptoms expression in borderline personality disorder (BPD), neural mechanisms driving treatment-induced symptoms recovery remain poorly understood. Therein, faulty brain activity (midline cortical areas) involved in personal identity processing, autobiographical memories and self domains have been identified in our pre-treatment fMRI study as potential treatment candidates for psychotherapy. In this view, the current follow-up fMRI study examines the effects of a revised version of interpersonal psychotherapy adapted to BPD (IPT-BPD-R) versus patients on waiting list (WL) and healthy controls (HC) on brain activity patterns in the brain target areas. We found that 18-month treatment with IPT-BPD-R was successful in improving borderline identity functioning (IDQ) which was mediated by downregulating hyperactivity in rTPJ, rACC and vmPFC. Better characterization of neural mechanisms mediating recovery from identity disturbances holds promise for developing and refining treatment modalities tailored to address more specific areas of borderline pathology.

1. Theoretical conceptualisations

In quest for more refined treatments to target specific neuropathology, research in clinical neurosciences has focused on neural mechanisms mediating therapy-induced amelioration of symptoms. Owing to improvements in neuroimaging techniques, it is now well-established that all treatments, whether pharmacological or psychosocial, have measurable influences on the brain structure and function. Accordingly, the traditional dichotomy of endogenous versus organic illness has been dispelled by the recognition that all changes in mental processes are accompanied by changes in the brain. Thus, all psychiatric interventions can be considered biopsychosocial in nature where a psychotherapy, beyond its psychological effects may prompt cerebral reorganisation within the area of insult to the brain, and likewise pharmacotherapy in addition to acting at neural-systems level may alter psychological states. In this view, the ultimate goal of all psychiatric treatments is to trigger neural processes of recovery in a manner that restores full function and potential of the injured brain. This is achieved through the mechanisms of neuroplasticity, wherein constituent elements of learning and memory allow the brain to receive novel stimuli and to make appropriate adaptive response to favour recovery [1]. In what follows, the theoretical and empirical literature on BPD is summarised, focusing primarily on identity disturbances in keeping with the scope of our study. To better characterize this domain of pathology, the next section follows with a description of the narrative-self, fragmented self, and the construct of autobiographical memory, developed as a direct measure of identity disturbances in the disorder.

1.1. Borderline Personality Disorder in DSM-5

BPD is a severe psychiatric disorder characterized by pervasive pattern of instability in affect, impulsivity, identity and interpersonal relationships [2]. Frequent self-damaging impulsive behaviours such as suicidal tendency, self-injury or substance abuse contribute to high morbidity associated with the disorder, and constitute the most useful indications for a correct diagnosis [3]. Accordingly, this psychiatric category is characterized by severe and stable functional impairment [4-6], reflected in low level of psychosocial functioning that tends to be lost over time, and in 80% of cases never regained [7].

With regards to the conceptual construct of the diagnosis, factor analyses have established a three-factor model with constituent elements including affective instability, behavioural dysregulation (impulsivity) and disturbed relatedness [4,8]. Thus, empirical evidence exists to support the underlying multidimensional structure of the disorder, characterized by three homogeneous components. Among the identified domains of dysfunction, the most prevalent and stable symptoms are affective dysregulation and interpersonal disturbances. The former is believed to constitute the core of borderline pathology [7, p.372], and is characterized by abnormalities in the processing and regulation of emotions. These are manifest in aberrant variability in affective states with frequent negative emotions in response to seemingly neutral stimuli, such as rage or anxiety [for a review 6]. Disturbed relatedness in turn, refers to relational style typically exhibited by individuals with BPD, which is distinctively characterized by turbulence and excessive fear of abandonment, speculatively resulting from impaired mentalization capabilities and elevated rejection sensitivity [3]. The most prominent aspect inherent to interpersonal disturbances is the notion of 'interpersonal hypersensitivity', evidenced in a bias toward negative perception of ambiguous expressions and reading others as untrustworthy, angry or deceitful [for a review see ref. 9]. This perceptual bias is likely to exacerbate the threat of social rejection, negative judgement, unfairness and mistrust of others [10-16].

Impulsivity in BPD is the least stable symptom domain, manifest in deliberate self-destructive acts of self-harm, suicidal communication with suicide attempts, and more general forms of impulsivity such as substance abuse, spending sprees, reckless driving, physical and verbal outbursts [17].

These three core domains of dysfunction are expressed to varying degrees in borderline pathology, wherein five out of nine DSM-5 criteria must be met for the diagnosis [8]. Moreover, this diagnostic category includes patients with or without stress-related paranoid ideations or chronic feelings of emptiness [18]. Thus, despite implying a statistically coherent construct, BPD population is characterized by abundant clinical variability with 151 theoretical possible ways of diagnosing the disorder [18,19]. As a result, patients' heterogeneity is disguised by the diagnosis, and assigning patients to a treatment deemed more efficacious than treatment as usual solely on the basis of their DSM classification arises many controversies [4,5]. Thus, a better insight into the mechanisms through which treatments achieve their therapeutic effects on the neural systems level holds promise for taping into the patient heterogeneity to ultimately refine the process of matching patients to interventions.

1.2. Identity disturbances in BPD

More relevant to the purpose of this study, DSM-5 defines identity disturbance as a core feature of BPD, characterized by defused identity and impaired self-direction (APA) [2]. The former refers to impoverished, poorly developed, and unstable self-image, which is typically associated with chronic feelings of emptiness, excessive self-criticism and dissociative states under stressful situations. The latter pertains to instability in values, goals, aspirations, interests and career plans that persists over time. Accordingly, the phenomenology of borderline identity is associated with eruptive shifts into states, characterized by distorted perception of reality, lack of clear concept of self-development, impaired ability to adapt to novel situations, and rapid changes in roles and relationships.

Inasmuch as borderline patients tend to identify with their momentary affective state, they develop discontinuity of self-experience over time, aptly termed as an 'atemporal mode of existing' [20]. It is characterized by constant switching from one present to the next, thereby excluding future and past as dimensions of object constancy, responsibility, bonding, guilt and shame. As a consequence, individuals with BPD are defined by what they are experiencing at the moment. Unable to gain distance from the present state, they are torn by emerging impulses, bursts of anger, addiction, self-harm and so forth. Although this mode of existing excludes the threatening uncertainty of interpersonal

relations, it is achieved at the price of a chronic feeling of emptiness, which characterizes borderline pathology. Immersed in an intense and yet shallow transitory present, they lack fulfilment, and desperately search for immediate reward from momentary thrills and pleasures, turning life into unconnected series of fragmented events without any historical progression [21]. Loss of past experiences to draw upon in making reflective decisions is also associated with behavioural dyscontrol and the lack of agency or authorship of life [22]. It appears as though instead of projecting themselves into the future, borderline patients stumble into it. Ultimately, the inability to integrate past and future into the present leads to impaired self-narrative, temporal fragmentation of the self, thereby hindering the development of a coherent sense of identity [20].

1.2.1. Impaired self- narrative and insecure attachment

Immersed in a told story of a lived life is the narrative self, aptly referred to as the inner witness to whom we talk to, and to whom we hold ourselves accountable for our intentions and actions [23,24]. Self-narrative, however, does not imply a creative work of a single author, but rather a collective and intertwined product of a complex interaction between first-, second- and third-person perspectives of many co-authors [25]. In this view, the inner witness entails a secure early attachment to important others, which evolves from the experience of mutual emotional attunement provided during holding, soothing and mirroring by the caregiver [26]. The securely attached child integrates the caregiver's representation of him into a coherent understanding of what it means to be an intentional being with wishes, needs and agency [27]. The shared history with the other is internalized by the child as implicit 'schemes of being-with-others', and provides a basic sense of life continuity and coherent narratives of oneself [28, 29]. Conversely, research shows that deficits in early social attunement often impair the child's reflective or representative functions, thereby precluding him from being able to ascribe meaningful and intelligible intentions, aims and motives to own and others' actions and behaviour [30]. Inasmuch as the representations of the self perceived by the child in the caregiver are threatening to his psyche, he withdraws from the mental realm [27]. Therein, in the process called projective identification, intolerable perceived mental states of the caregiver are expelled and projected onto others, where they can be despised and fought. All this means that mental states of others remain alien, unlabelled and confusing to the

individual, thereby predisposing him to ascribe hostile intentions to others, and fundamentally foster insecurity in social functioning. To the extent the insecurely attached individual has difficulties in stepping inside the mind of another and understanding the continuous narrative commentary on one's experiences linking the past, present and future, his autobiographical memory and narrative identity are seriously impaired. Drawing upon research, majority of borderline patients were found to exhibit overinvolved-preoccupied or avoidant attachment patterns (75–90%) [31,32], which allows to conceive of identity disturbance in BPD as a disorder of early social attunement, wherein deficient inner representations of others preclude from establishing coherent narrative identity. Moreover, the caregiver's inability to mirror, label and sooth emotions of the child explains why borderline patients are typically not able to adequately perceive, interpret and self-regulate their emotional states [33].

In sum, impaired reflective and empathic skills in borderline individuals explain not only identity disturbances characterizing this diagnostic category, but also inability to self-regulate and establish realistic relationships.

1.2.2. The fragmented self in BPD

The implicit self constantly re-evaluates and negotiates the meaning of our past actions, and anticipates the outcome of future projects to ensure the unity of a personal narrative enacted in the course of life [34, p. 3]. Thus, the unity and coherence of a personal story essentially depends on higher-level, self-referential processing of an individual, necessary to integrate contradictory aspects into an overarching and stable sense of selfhood, and to rule out divergent strivings. Achieved in this process a coherent sense of self-concept provides historical continuity that is essential for the development of a stable identity. One of the functions of self-referential processing is the ability to shift perspectives away from the immediate present to make mental time travel possible [35]. This requires imaginatively projecting oneself through time into a mentally simulated event, either in the past or in the future [36-38]. In neural terms, self-projection and self-referential processing are supported by the same core brain network activated in resting states [39], and overlap with cortical midline structures [40]. Accordingly, deficits in self-referential processing might lead to impaired forms of self-projection.

These deficits, interfere with developing a coherent synchronic self, giving rise to identity fragmentation, that is manifest in autobiographical memory disruptions [41].

Notably, self-referential processing appears to be impaired in majority of BPD patients (60–90%) [42]. Being unable to gain a reflective position beyond their present emotional arousal to monitor ongoing thoughts for coherence and unity, they engage in endless repetition of the same affective states. Therein, rapid shifts in mood states activate mood-specific autobiographical memories and images, as posited by the theory of context-dependence of memory in cognitive psychology [43]. In this view, the tendency to switch between extreme emotions leads to incoherence of mood-related memories and deficient identity, where an individual may feel like being several different persons defined by a particular mood state. As a result, they exhibit a fragmentation of the narrative self, characterized by rapid shifts in the concept of oneself, goals, values, roles and relationships with no sense of object constancy over time and across situations [44]. This may lead to a painful sense of inauthenticity and pretend, frequently reported by this clinical population [45]. To compensate the lack of stable self-concept, borderline patients tend to change their identity on the basis of who they are with, assuming a chameleon-like appearance [44, p. 352]. The felt lack of inner identity evokes in a diagnosed individual a desperate need for the other to give a sense of unity and continuity to a life made of disconnected episodes. Since the other is needed to establish a sense of inner identity or else, as a carrier of intolerable own aspects projected onto the person, the loss of intimate social relationships evokes a loss of the very self [45]. It is therefore conceivable that individuals with BPD, who fail to maintain intimate social relationships with those who come and leave their lives in a ceaseless succession, are particularly prone to fears of abandonment and frequently suicide attempts.

1.2.3. Autobiographical memory impairment in BPD

More pertinent to the present study, the fragmented self is associated with marked discontinuity of autobiographical memory in BPD patients, showing gaps and inconsistencies in recalling own experiences form the past, in some cases even not being able to remember several years of childhood or to recognize themselves on an old photo [46,47].

Therein, subjective, experiential raw material is processed into semanticized memories and assembled into a piece of autobiography, which collectively constitutes a coherent moment-to-moment narrative identity with temporal extension [41]. Formed in the process autobiographical memory constitutes a complex mental system responsible for recall of past events, experiences and information, thereby allowing the self to feel that it has existed in the past and will exist in the future [48]. Thereupon, the construct of autobiographical memory has been used as a novel theoretical framework in research efforts to directly measure identity disturbances in individuals with the disorder. In other terms, a narrative account of the self focused on semantic contents of memory retrieval provides an index of autobiographical memory functioning, and hence reveals the structure of personal identity. Accordingly, a wealth of evidence using the construct of autobiographical memory evidenced blind spots or mental holes in personal stories told by borderline patients, who might not remember what they did or said in a condition of emotional arousal [49-51].

These deficits in autobiographical memory are explained, at least in part, in terms of the patients' susceptibly to dissociate [47]. Dissociative experiences refer to 'conscious forgetfulness [52] of traumatic or adverse events, which interfere with the patients' ability to integrate perception, affect, memory and identity into a coherent and unified sense of self-narrative [53]. Inasmuch as autobiographic memories are distressing to the individuals' psyche, they are stored in the form of sensory fragments without a coherent narrative, causing disruptions of consciousness and memory, thereby resulting in a fragmented sense of self. Another psychological phenomenon known to undermine the coherence of autobiographical memory characterizing this clinical category is the formation of overgeneral memories, typically retrieved in categories as opposed to specific personal memories [47]. Both phenomena result in a failure to activate trauma-related memories and therefore are believed to serve as a coping strategy against recall of painful memories. Although this strategy appears to be effective in trauma-related disorders, it is also highly maladaptive in that it is achieved at the cost of forming a coherent piece of autobiography [54]. On a positive note, various treatment strategies exist to treat BPD, and out of those Interpersonal Psychotherapy (IPT) has been adopted to address dysregulated self in patients with the disorder (IPT-BPD).

Herein, the next section follows with an overview of evidence-based treatments currently available for the disorder, with special focus given to IPT in view of the current study.

2. Psychosocial treatments for BPD

When BPD first entered the DSM-III, the disorder was defined as a 'behavioural pattern resistant to traditional psychotherapy' [55]. To date, psychotherapy constitutes the gold standard of care with a range of psychotherapeutic approaches designed specifically for the disorder [56]. Specific forms of psychotherapy seem to be beneficial for at least some of the problem areas frequently reported in patients with the disorder. Among them five are established evidence-based treatments, namely Dialectic Behavioural therapy (DBT), Mentalization Based treatment (MBT), Transference- Focus psychotherapy (TFP), Schema- Focused therapy (SFT) and Systems Training for Emotional Predictability and Problem Solving (STEPPS) [57].

DBT is the most researched and refined treatment, developed for suicidal patients whose pathology is posited to result from a transaction between highly vulnerable individuals and environments invalidating of their sensitivity [58-60]. Embracing the deficit in self-regulation model of the disorder, interpersonal skills, and distress tolerance, DBT integrates validation strategy to instil skills and behaviours that enable the person to become more mindful, and to manage emotions and relationships more effectively.

Embedded in the theory of attachment, MBT operates on the mentalization deficit model of borderline pathology, that is manifest in the difficulty to comprehend own and others' states of mind [61,62]. It posits that interpersonal and affective disturbances are aetiologically related to inadequate mirroring of emotions by the caregiver and early trauma experienced by constitutionally vulnerable individuals [63,64]. In this view, MBT sets out to promote the ability to mentalize in the context of attachment relationships, wherein lies the mechanism of change. Although no evidence exists to show that one treatment is more effective than another, DBT and MBT are the most researched, refined and widely adopted approaches with the largest evidence base for BPD treatment [61,62]. Efficacy studies have shown that these forms of psychotherapy seem to be superior to treatment as usual with stable over time effects in some clinically relevant problems of borderline personality disorder.

Schema focused therapy (SFT) [65] and transference therapy (TFP) [66] both focus on the structures of the mind, however, whilst the former addresses the developmental schemas, the latter is directed at understanding of unconscious object relations, enacted by the patient with the therapist. STEPPS is a cognitive- behavioural skills training approach developed to address the growing need for outpatient treatment program [67]. It combines cognitive-behavioural techniques and skills training with a systems component (persons in their system e.g., family members, significant others, health professionals) to provide BPD sufferers and closely allied persons with language to communicate effectively about the disorder, and skills to manage emotions and behaviours.

Thus, all evidence-based psychosocial treatments focus primarily either on internal states or behaviours. Moreover, they are highly structured and theoretically coherent to the therapist and the patient, directed at fostering strong attachment relationship and improving compliance. Notably, these shared characteristics are believed to account for effectiveness of all aforementioned psychosocial treatments rather than their specific therapeutic postulates [56].

2.1. Interpersonal Psychotherapy for BPD (IPT-BPD)

It is generally agreed that BPD is a disorder of dysfunction in self-regulation, particularly manifest in the context of social and interpersonal relationships [68]. Accordingly, the DSM-5 characterization of the disorder includes a pattern of unstable and intense interpersonal relationships with frantic efforts to avoid abandonment, inappropriate intense anger or difficulty controlling anger in social and relational contexts [2]. This allows to speculate that fostering the ability to establish constructive relationships with others is essential in ameliorating self- regulation with array of BPD symptoms. In this view, interpersonal functioning is a key therapeutic postulate of IPT, making it a potentially important clinical avenue in the treatment of the disorder [69].

Rooted in the theory of attachment [70,71], IPT was originally developed as a treatment for depression [72,73] and subsequently modified to treat borderline patients [69]. Its theoretical heritage posits disorganized attachment system at the basis of BPD pathology, which is expressed in exaggerated reactions of the insecurely attached infant, such as

fearfulness about dependency needs, clinging, fear of abandonment and constant monitoring of the proximity of the caregiver [74,75]. Within this framework, disorganized attachment system in infancy serves as a prototype for future relationships, and notably was found to be predisposing of later borderline pathology [76,77]. Accordingly, individuals with the disorder typically exhibit a hypersensitive attachment system that is too easily triggered when faced with interpersonal stress [78]. This results in demanding behaviours and seeking out others for protection. Operating on the thesis of disorganized attachment as a key element at the basis of affective and relational disturbances in BPD allows to speculate that symptomatic recovery entails improved regulation of interpersonal relationships through changes in neuropsychological processes underpinning social experience [79]. It is therefore intelligible to theorize that addressing relational disturbances might ameliorate interpersonal functioning, mental states and augment affect regulation. Therein lies the posited mechanism of therapeutic change under IPT.

However, treating lifelong personality dysfunction is bound to be more challenging than treating patients with depression who, prior to experiencing an acute episode of the disorder, might have been functioning well. In this view, the IPT-BPD format departs from the standard acute treatment for major depression, and adopts a treatment focus related to unstable and volatile self-image as a prototypical feature of the disorder and exacerbating source of affective and interpersonal disturbances [69]. To treat problem areas specific to borderline pathology, the IPT-BPD manual is characterized by the following features of adaptation (1) conceptualization of the disorder, (2) chronicity of the disorder, (3) difficulties in forming and maintaining the treatment alliance, (4) length of the intervention, (5) suicide risk, and (6) termination. The treatment recognizes that overtime BPD sufferers tend to confuse the longstanding diagnosis with the self, owing to the chronic nature of the disorder. Herein, IPT raises in patients the exciting prospect that in the course of a relatively brief therapy they might be able to shed symptoms that persisted throughout adulthood. This is somewhat consistent with literature reporting that majority of BPD patients experienced a substantial reduction in their symptoms, with improvements mainly in impulsive behaviours and affective instability. Data supports that 75% of patients who required hospitalization, achieved remission after 6 years by standardized diagnostic criteria [80].

Notably, social and interpersonal function seems less responsive to treatment with lives of sufferers severely incapacitated by inability to form meaningful relationships with others [81]. This suggests that a therapy which places interpersonal disturbances as a central component of clinical practice may offer a way forward in treating aspects of BPD, is likely to improve outcomes for this diagnostic group, and make recovery possible. To achieve this, IPT adopts the medical model, defining the disorder as a chronic, yet treatable illness that is not the patient's fault [82]. This approach emphasizes the importance of resolution of the iatrogenic role transition, where patients come to understand how the disorder has inhibited their interpersonal functioning. Equipped with more adaptive interpersonal skills, they are able to yield success experiences, and as a consequence symptom and maladaptive interpersonal behaviours become ego-alien. This rethinking of lifelong personality as an alien and removable syndrome puts a positive slant on the diagnosis instilling in patients the expectation that reforming lifelong character is possible.

Key indicates of utility of the modified version of IPT treatment include the development of therapeutic alliance, interpersonal skills and systematic attention to monitoring mental states in relation to interpersonal functioning [82]. Although these are considered "common factors" of psychotherapy, unlike cognitive behavioural therapies which target cognitions, the overarching focus of IPT is on affective and interpersonal responses [83]. Inasmuch as IPT focuses on the patient's life outside the psychotherapist's office without interpreting dreams or transference in the therapeutic dyad [84], it also differs from the clinical stance of a psychodynamically oriented therapy [85,86]. Its unique feature is that IPT offers a platform, where interaction matrix of attachment is recreated to shed critical light on the patient's current life 'out there' passing over his or her internal realm. In this view, the therapeutic relationship replicates other relationships the patient has outside the office to increase the likelihood of solving "real life" interpersonal issues. Fostering interpersonal skills, such as effective expression of anger, confrontation and self-assertion, will create new possibilities for better social functioning. The basic premise of IPT is that if patients, who have never felt in control of their emotions or their interactions with others can generate success experiences, it will have a powerful therapeutic effect on improving their lives and mood.

In this view, disruptions in the interactions and experiences with others in relation to behaviours and moods are evoked and carefully examined. Emphasis is placed on the ability of the therapist to maintain alliance and repair possible sudden ruptures, bearing in mind the elevated interpersonal hypersensitivity that typically characterizes this clinical category. Although the key aspect of the therapy is interpersonal functioning, the focal area is fundamentally regulation of the self through social experience. By way of example, when faced with interpersonal arousal individuals with BPD typically are unable to represent their own self separately from their representations in other's mind [79]. Therein, careful scrutiny of actions of the self and others as initiated and animated by mental states is posited to instil a more robust self in the patient with better awareness of agency in social interactions. Thus, IPT posits regulation of the self within interpersonal interactions as the foreground of its therapeutic approach, tailoring it to the disturbance of the self in relation to others as the core pathology of the disorder [87].

Despite the tenable rational for adopting IPT in the treatment of BPD patients, it is yet to be established whether it can be effective in elevating borderline symptoms. To measure how much interpersonal change the patient and therapist feel has been accomplished in work on a specific problem area, the Interpersonal Psychotherapy Outcome Scale is used [88]. Heretofore, there is a dearth of relevant research with one study reporting significant improvement in five out of ten patients who completed the treatment [89]. The adaptation of IPT was also tested by our research group, randomising 55 patients with BPD in 32 weeks of treatment with either fluoxetine plus clinical management as a standard treatment or fluoxetine plus IPT for BPD [90,91]. The combined therapy was shown to be more effective in elevating interpersonal and affective disturbances, impulsivity as well as overall psychological and social functioning. Notably, these improvements correlated with reduction in core symptoms of BPD in the experimental group.

Given that BPD is the first Axis II disorder to which IPT has been applied, the potential utility of this therapy for the disorder is yet to be established by outcome research. Nevertheless, strong theoretical rational and the practical ethos of IPT warrant future research efforts to delineate the underlying mechanism of action and discern therapeutic components of the therapy.

First and foremost, BPD it is often comorbid with major depression and dysthymic disorder [92], and was even suggested to be a subtype of chronic mood disorder [93]. By way of example, a review of 16 studies where structured or semi-structured diagnostic instruments were used to establish co-morbidity and revealed that 61% of patients diagnosed with BPD had also major depressive disorder, whereas 29% had panic disorder with agoraphobia and 13% substance misuse [94]. It is therefore tenable to suggest that an evidence-based treatment for mood disorders is likely to be efficacious in ameliorating borderline symptoms. Furthermore, a treatment which places awareness of agency in interpersonal life as a central thrust of its therapeutic endeavour, and a better regulated, more robust self in relation to others as its major therapeutic postulate is potentially an important clinical avenue for BPD patients.

In sum, the practical ethos of IPT, its strong theoretical rational and hints from empirical research on factors accounting for variance in treatment outcome warrant further research to elucidate the underlying neural mechanism of IPT-induced amelioration in borderline disturbances of the self. In what follows, I review all-to-date research on the posited neural mechanism of BPD symptoms expression and recovery with a special focus on identity disturbances, to allow interpretation of the current study in the light of the existing literature.

3. Neuromarkers of symptoms expressions and recovery in BPD

The long-held clinical knowledge that psychosocial interventions can alter mental and psychological states is now characterized in neural terms as measurable mechanisms of treatment- induced brain plasticity. Neuroimaging techniques index cerebral blood flow or glucose metabolism, thereby providing a mean of measuring patterns of neural plasticity driving post-treatment amelioration of symptoms. Among commonly used techniques are functional magnetic resonance imaging (fMRI), 18fluorodeoxyglucose positron emission tomography (FDG-PET), and 99m technetium hexamethylpropyleneamineoxime single photon emission computed tomography (99mTc-HMPAO SPECT) [see ref.1 for a detailed review]. More relevant to the current study, task-based functional magnetic resonance imaging (t-fMRI) is a potent imaging modality to significantly advance the study of neural

recovery processes. Its constituent core element is a paradigm, defined by a functional measurement with a stimulation adjusted to the brain area under investigation. Typically, GRE T2*-weighed echo planner images (EDI) are rapidly acquired during completion of a defined motor or sensorimotor, language or another cognitive or visual tasks in the MRI scanner [for a more in-depth description of fMRI see ref.17]. Inferences on brain regions/networks functionally involved in a target tasks are made by comparing local changes in cerebral blood flow (CBF) during execution relative to resting state. Then, multiple pre-, and post- therapy scans are compared against brain activity patterns in other active treatment groups and a no-treatment waiting-list group to ultimately characterize the specificity and extend of neuroplasticity induced by the treatment under study [1]. Understanding how treatments achieve their therapeutic effect on the neural level is particularly important for patients with BPD, traditionally deemed difficult-to-treat.

3.1. Neural mechanism of symptoms expression

In neural terms, the pathology of BPD is best understood as subtle defaults across frontolimbic networks. Neuroimaging literature has highlighted dampened activity in regions of the prefrontal cortex (PFC) coupled with elevated activity within limbic structures in studies probing emotional and cognitive processing [for a review see ref. 10]. The most consistent findings report hyperactivity of the amygdala [11-13] and insula [13], and hypoactivity in the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC) and frontopolar cortex (FPC) [10]. By way of example, whilst using destruction strategy to control emotional responses to adverse images, BPD patients exhibited dampened activity in the ACC coupled with hyperactivation in the superior temporal sulcus and superior frontal gyrus than did control [95-97].

Increased activation in the PFC occurring after inducing negative emotions was interpreted as effortful yet insufficient attempt to control intense emotions. Moreover, experimentally induced pain in actively self-harming patients led to deactivation of the amygdala [10] and lower posterior cingulate cortex (PCC) connectivity with the dorsolateral prefrontal cortex (dlPFC), allowing to speculate that self-injury represents efficient, nonetheless highly dysfunctional attempt to regulate disturbed emotions [17,

18]. Taken together, neuroimaging evidence have led to the thesis that patients with BPD exert diminished recruitment of frontal brain regions involved in regulatory and inhibitory processes over elevated limbic activity in emotional processing [14, 15].

Drawing on research into biomarkers of interpersonal hypersensitivity inherent to interpersonal difficulties in BPD, imaging data in social cognition have identified increased and prolonged activity in the amygdala [98, 99] and the anterior insula [100,101], thereby advancing the thesis of elevated bottom-up emotion generation processes [102]. Herein, the functional connection between amygdala and ACC, and increased anterior insula activity is the silence network, which gives a stimulus the ability to be selected in early bottom-up processes of evaluation for valence and salience [103]. In addition, disturbed mesolimbic circuitry is believed to mediate poor social reward experience in BPD, presumably resulting from appraisal of others as threatening, deceitful and untrustworthy. Therein, alterations in brain reward system activation within the pregenual ACC, ventral tegmental area and ventral striatum in response to social stimuli possibly indicate a deficit in differentiation between reward and non-reward anticipation [104]. Other line of evidence come from trust game studies that involve processing of social stimuli and detection of unfairness mediated by the insula. Whilst the activity of insula in healthy controls tends to fluctuate according to the perception of fairness of the transaction, in BPD subjects it remains hyperactive throughout the experiment [105]. This might indicate a deficit in perceiving the violation of social norms [106] and explain some of the difficulties in social functioning.

Neuroimaging data on biomarkers of impulsivity points to diminished recruitment of frontal regions that provide control or 'brakes' for excessive bottom-up activity within limbic regions in emotional contexts [107] and exposure to stress [108]. In inhibitory control tasks BPD patients failed to activate posterior-medial OFC and the dorsal and subgenual ACC compared to selective activation of the posterior-medial OFC, dorsal ACC, dlPFC, amygdala and hippocampus in healthy controls. Reports of dampened activity in ventromedial PFC (including medial OFC and subgenual ACC), and elevated extended amygdalar ventral striatal activity was found to correlate with decreased constraint and increased negative emotion, respectively [109].

Taken together, evidence supports a model of impaired prefrontal inhibitory function in BPD patients in emotional contexts during a task requiring motor inhibition. Frontolimbic abnormalities in BPD pathology were echoed in a recent meta- analysis, which reported hyperactivity within amygdala, hippocampal and posterior cingulate cortex, together with hypoactivity of the bilateral dlPFC in response to seemingly neutral stimuli [110].

3.1.1 Neuromarker of identity disturbances in BPD

Historically, the question of the self has long intrigued philosophers and psychologists. To date, the phenomenon is examined using cognitive neuroscience research tools such as neuroimaging in efforts to delineate its cerebral organization [111-115]. Thereupon, recall of autobiographical memories has been used as an indirect index of the level of identity integration and coherence [116-118]. It entails a process of reflective thinking through which links between disparate elements of own life and the self are formed [119-123]. Neuroimaging studies using tasks consisting of recall of specific life events in healthy subjects highlighted a crucial role of posterior cingulate cortex (PCC), left medial prefrontal cortex (lmPFC), and hippocampus with surrounding regions [124-131]. Furthermore, changes in activity patterns in relation to memories of life events were detected in the prefrontal cortex (PFC) (a region in the dorsal extent of the inferior frontal gyrus and a region of the right frontal polar cortex), lateral and medial posterior parietal cortex, inferior parietal lobule complex [132-134], temporoparietal junction (TPJ), and cerebellum [125,135-137].

Albeit the core of borderline pathology, neural mechanisms of self-disturbance remain poorly characterized, relative to other problem areas of the disorder [138-140]. Thereupon, few fMRI findings using social tasks revealed impaired self-other differentiation [141], with poorly differentiated self-referential cognitive and emotional processes [142]. These deficits were mediated by a hyperactivation in brain areas underpinning of social cognition, namely the mPFC considered a neural marker of hypermentalization [143], the temporoparietal junction (TPJ), several regions of the frontal pole, the precuneus and the middle temporal gyrus. Whilst TPJ has been shown to mediate self-other discrimination [144-145], the precuneus is believed to be involved in self-consciousness and self-awareness [146], and angular and lingual gyrus in

accessing a mental picture of another [147]. In contrast, healthy controls in aforementioned studies evidenced greater activation in visual, sensory, motor and mirror neuron regions. These activity patterns allow to speculate that individuals with BPD may utilize more complex strategies that are less organized for representing self and others.

More relevant to our study, Beblo *et al*., [138] compared brain activity patterns in 20 BPD patients and healthy controls during recall of resolved versus unresolved live events, stimulated by cue words extrapolated from an Autobiographical Interview. Whilst all autobiographical memories referred to negative experiences, the former were perceived as settled and not emotionally arousing during recall, whereas the latter still evoked intense emotional reactions. Data revealed elevated neural activity patterns during recall of unresolved versus resolved life events in patients with BPD, but not in controls. These were evident in significant bilateral activation of frontotemporal areas including the insula, amygdala, the ACC, the left posterior cingulate cortex (lPCC), right occipital cortex, the bilateral cerebellum and midbrain. Identified changes in brain activity patterns were interpreted as increased, yet insufficient attempt to regulate emotional arousal during the recall of unresolved life events in the clinical group. Notably, a follow-up study over one year on the same subgroup of BPD patients revealed a substantial decrease in the right, relative to the left hemispheric activation of the brain areas (temporo-frontal neural activation patterns) believed to process autobiographically relevant, highly adverse or traumatic and anxiety-arousing information [140].

In a similar study, pictures from the Thematic Apperception Test (TAT) versus neutral pictures were used as a visual stimulus to evoke aversive autobiographical memories to characterize underlying neural activity pattern in BPD patients [139]. In contrast to healthy controls, the clinical group evidenced similar activity patterns in orbitofrontal, cingulate, and frontal areas under both conditions. Moreover, identified heightened activity in the PCC and temporal areas in borderline patients were indicative of selective attention deficit in autobiographical memory retrieval and a self-referential information processing. Other similar studies have highlighted altered dlPFC activity in borderline patients [131,148,149] mediating cognitive control across self-referential and non-self-referential processes [150].

3.2. Neural mechanism of treatment-induced recovery from BPD

Neuroimaging literature has recently begun to characterize mechanisms driving cerebral recovery within specific circuits mediating post-treatment amelioration of symptoms in patients with BPD. Latest review of all here-to-date functional MRI findings of post-therapy brain changes identified seven relevant studied with six focusing on neuroplasticity under DBT and one under TFP [152]. Early pilot studies examined whether improvement in emotion regulation under DBT was mediated by alterations in neural underpinnings. In this view, six unmedicated female patients with BPD matched against six healthy controls were scanned five-times before, during and after a 12-week in-patient treatment program [153] in emotional context (International Affective Picture System) [154]. Functional changes to negative stimuli were evidenced in limbic and cortical regions including decreased activity in ACC, PCC, insula, left amygdala and both hippocampi in four treatment responders relative to controls. Goodman *et al*. [155] examined pre-and-post DBT effects of 12-month course of treatment on amygdala activity and overall emotion regulation in unmedicated BPD outpatients matched to healthy controls. The results corroborated the thesis of treatment- induced amygdala normalization, showing significant reduction in overall amygdala activation, which was particularly notable in the left hemisphere and during repeated emotional pictures. Unsurprisingly, attenuated activity patterns were associated with improved overall emotion regulation (DERS). Whilst encouraging, results of these studies are interpreted with caution as the former did not use standardized instruments to divide patients into responders and non-responders, and the latter did not include a clinical control group necessary to draw borderline-specific conclusions.

Other studies focused on alterations in neural correlates of various emotion regulation strategies under DBT and related symptoms improvement. By way of example, Schmitt et al. [156] indexed changes in cerebral correlates of reappraisals under a 12-week inpatient DBT program in 32 female DBT patients, relative to 24 healthy control participants and a clinical control group of 16 BPD patients. Consistent with previous findings, post-treatment scans evidenced reduction in the amygdala, insula, dlPFC and ACC activity patterns.

Furthermore, reappraisal of negative stimuli after DBT was mediated by increased connectivity of ACC to medial and superior frontal gyrus, superior temporal gyrus and inferior parietal cortices. Consistent findings exist to support that a 12-week residential DBT-based treatment alters neural correlates of distraction manifest in a stronger use of a fronto-parietal emotion regulation network and attenuated limbic hyper-reactivity [157]. Identified changes in activity patterns might reflect a shift from emotional to more cognitive processing during arousal, indicating an improved emotional susceptibility during distraction strategy. Taken together, these studies posit that learning affective control strategies under DBT may trigger adaptive reorganization within neural underpinning of emotion regulation, thereby lending support to the skills deficit model of DBT. However, firm conclusions cannot be drawn from these as patients received combinations of drug subtypes which was previously shown to attenuate emotional responses [110].

Given that DBT targets response inhibition deficit implicated in self-harm, one study set out to establish whether patterns of activation in neural correlates of target deficits may isolate markers of treatment response and attrition [158]. To achieve this, 29 actively self-harming BPD patients (90.30% females) were scanned before and after 7 months of DBT while performing the Scarborough nonaffective Go/No-go motor inhibitory control task. Reduced incidence of self-harm was found to correlate with attenuated levels of activity in dlPFC before therapy with the highest increases in activity in this region after 7 months of treatment. Moreover, increases in the right dlPFC activity was associated with lesser incidence of self-harm, even when improvements in BPD symptoms severity, depression and mania were controlled for. Conversely, patients who dropped out from the treatment exhibited greater pre-treatment activation in the medial PFC and right inferior frontal gyrus relative to treatment completers, possibly indicating a lesser recruitment of inhibitory control processes by the PFC. It has therefore been shown that pre-treatment activity patters in areas of the PFC mediating impulse control may be associated with treatment responses to DBT and attrition from therapy.

One report of TFP-induced neuroplasticity highlighted alterations in frontolimbic neural activation behind symptom amelioration in domains of constraint, affective liability and aggression, as well as predictors of treatment response in BPD [159].

Pre- and post-treatment scans (10–14 months apart) during emotional-linguistic go/no-go paradigm revealed post-TFP relative increase in activation within dorsal prefrontal areas (dorsal anterior cingulate, dorsolateral prefrontal and frontopolar cortices), and relative decrease in activation within ventrolateral lPFC and the hippocampus. Therein, heightened activity in the left dorsal ACC and left posterior-medial OFC/ventral striatum activation positively correlated with clinical improvement in constraint and affective lability, respectively. Corroborating previous data, activation in the right amygdala/parahippocampal was found to negatively correlate with improvement in affective liability. Thus, the study lends support to the thesis that psychodynamically oriented TFP achieves its therapeutic effect on the neural level by altering activity in the frontolimbic circuitry.

Beyond advancing the thesis of frontolimbic imbalances as a constituent element of disturbed circuitry in BPD, preliminary data elucidates possible mechanism induced by psychotherapy for BPD at the brain level to achieve therapeutic effect. Taken together, fMRI data supports that successful DBT alters neural underpinnings of emotion regulation, whilst TFP downregulates key neural circuits of impulsivity. This is achieved through downregulation of neuronal activity within the insula and amygdala, coupled with differential recruitment of prefrontal areas, mainly OFC, ACC and dlPFC, together with enhanced functional connectivity between limbic and prefrontal regions. It is therefore tenable to hypothesize that different psychotherapeutic models are unlikely to entail a specific neural mechanism of change, although drawing firm conclusions from presented data is hampered by low power, small sample size, generalizability limitations and pilot nature of the studies. Nevertheless, statistically significant results warrant research efforts to discern key neural circuits mediating amelioration of other domains of dysfunction, namely borderline self-disturbances. This provides rational to the pre-post-treatment fMRI study presented in the following sections.

4. Pre-treatment fMRI study

The limited evidence in previous literature was echoed in an fMRI study conducted by our research group on brain activity patterns in 24 BPD patients with identity diffusion performing the autobiographical memory task comprising recall of resolved and

unresolved life events [151]. The pre-treatment fMRI study was set out as a part of a bigger research to index differences in brain activity pattern in patients with DBP versus healthy controls during a task of recalling autobiographical memories (an indirect measure of identity integration) by comparing resolved to unresolved life events. Identified areas of altered activity are used in the current study as baseline to measure cerebral reorganisation within target areas induced by 10 months of treatment with IPT-BPD-R. It was hypothesised that DBP patients characterized by identity diffusion, including lack of internal consistency and constancy, would exhibit different brain functioning during the recall of crucial vital events compared to healthy subjects. The level of identity integration in patients and controls was assessed with the IDQ score, which evidenced a marked difference between the groups. Our imaging data revealed significant differences in brain activity patterns in specific areas in patients relative to healthy controls including the insula, ACC, mPFC, dlPFC and TPJ.

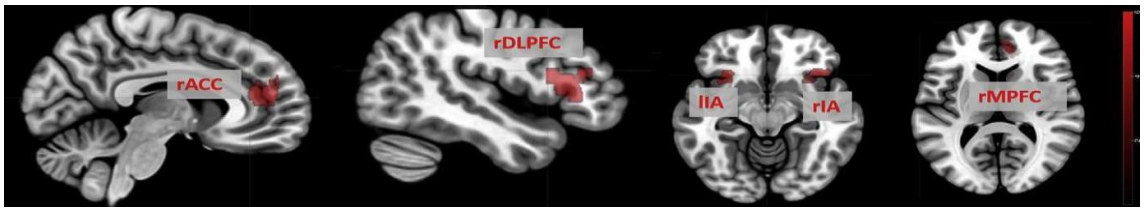


Fig. 1. Sig neural activation in group analysis: patient group vs control group for the contrast resolved keyword condition vs neutral keyword condition. ACC: anterior cingulate cortex, Al: anterior insula, DLPFC: dorsolateral prefrontal cortex, MPFC

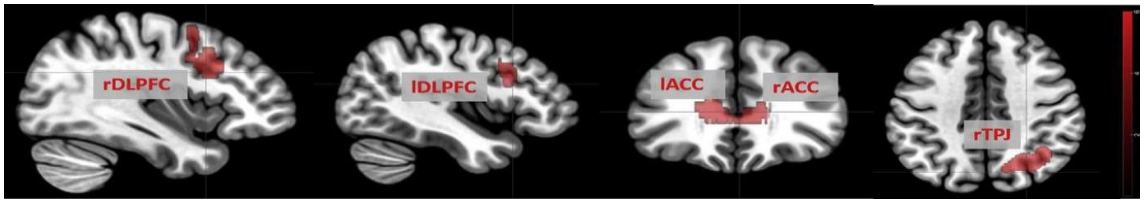


Fig. 2. Sig. neural activation in group analysis: patient group vs control group for the contrast unresolved keyword condition vs neutral keyword condition. ACC: anterior cingulate cortex, DLPFC: dorsolateral prefrontal cortex, TPJ: temporal parietal junction, r: right, l: left. The colour bar indicates t-values

With regard to resolved life events (see Fig.1), there was an increase in brain activity in the right ACC, right mPFC, right dlPFC and bilateral insula in patients with DBP relative to controls. Unresolved life events (see Fig.2) were associated with hyperactivity in bilateral ACC, bilateral dlPFC and right TPJ in patients relative to healthy subjects.

Notably, some areas of elevated activity including the ACC and dlPFC overlap in both conditions in the clinical group. The former is involved in attention and emotion processing, often described as an integration point of emotional and attentional aspects of incoming information from the body [160]. It was also found to be involved in self-regulation processes and adaptability to the environment [161]. The latter is typically involved in memory processes and recall of past events [162]. Accordingly, dlPFC was found to mediate the reconstruction of details concerning past episodes in order to mentally reexperience situations in their original context [163]. More relevant to our patient population, evidence exists to support the central role of ACC and dlPFC in creating personal narratives subservient of a stable sense of self and a coherent identity formation [164, 165]. Elevated activity pattern within these regions was interpreted as an attempt to exert cognitive control over negative affect [165]. In the light of given literature, ACC and dlPFC hyperactivity triggered by both resolved and unresolved events might reflect an effortful yet ineffective attempt to reconstruct a coherent narrative of significant life events whether resolved or less. This allows to speculate that patients with BPD are characterized by the tendency to experience most of their life events as poorly integrated on both emotional and cognitive level. Alternatively, one might also argue that elevated activity patterns in our study can be explained by the patient's tendency to overgeneralize autobiographical memories, typically retrieved in categories as opposed to specific personal memories [47]. Since hyperactivity results in a failure to activate trauma-related memories, therefore is believed to serve as a coping strategy against recall of painful memories. This strategy appears to characterize trauma-related disorders, where it is achieved at the cost of forming a coherent piece of autobiography [54]. The insula, mPFC, and TPJ were differentially recruited in the experimental conditions. More specifically, mPFC and insula evidenced a higher level of activity in patients with DBP than controls during the recall of resolved life events and related keywords, while TPJ showed elevated activation in patients with DBP compared to controls during the recall of unresolved life events and related keywords. These brain areas of altered activity patterns have received increasing attention in neuroimaging literature for their role in self-related processes. Therein, mPFC was found to be involved in the processing of self-related information subservient of constructing coherent personal identity [166], and in mentalization [167].

Our finding is further corroborated by evidence of altered neural activity in patients with DBP in regions that contribute to the processing of self-related information, mainly the mPFC [168]. The hyperactivity of mPFC might also explain the tendency of these patients to over-interpret and over-attribute their mental states and those of others, as well as the difficulty of processing meaningful information in situations of emotional arousal [169].

The insula was shown to process various aspects of perception, mainly in the realm of subjective affectivity associated with internal bodily states [170]. Accordingly, it is likely to be activated by tasks involving perceptive states and salient emotions [171]. In our study, the bilateral insula together with mPFC evidenced elevated activity in the resolved life events condition. This allows to speculate that these events cannot be considered effectively resolved and integrated into a coherent narrative of one's life in this patient population.

TPJ is implicated in the ability to mentalize, that is to understand mental states and thoughts of others, known as the theory of mind [172]. Our data revealed hyperactivity pattern in this brain area in response to unresolved events. This allows to speculate that unresolved experiences acquire a different meaning for our patients eluding to negative experiences in interpersonal functioning. Given that impairment in this domain is associated with mentalization deficit in DBP, hyper-recruitment of TPJ might be interpreted as a compensatory activity. Notably, TPJ is the only area of the brain that showed significant correlation with the IDQ score in our sample, positing its role in identify functioning of BPD patient population. Finally, our results of hyperactivity within the insula, mPFC, and TPJ is consistent with evidence across other disorders such as schizophrenia and autism, characterized by deficits in emotional awareness and mentalizing processes [172, 173].

Dearth of research on autobiographical memories in DBP patient population, differences in methods and design of experimental tasks hamper meaningful interpretation of our findings in the light of existing literature. There are three here-to-date studies on autobiographical memories in DBP relative to controls [138-140]. Our results are in contrast with those of of Beblo *et al.,* [138] and Driessen *et al.,* [140], while they are more consistent with data reported by Schnell and colleagues [139].

The former two showed elevated activity in the insula, the right OFC, the right temporal lobe, amygdala and the cerebellum in unresolved live events relative to resolved, but not in resolved relative to neutral events. Different findings in our research might be explained by methodological differences between the two studies. On the other hand, the data reported by Schell and colleagues [139] is somewhat more consistent with our findings. Therein, patients showed hyperactivity in the pre-confronted-cingulate brain areas in response to autobiographical and neutral stimuli, lending evidence to our thesis that individuals with BPD tend to experience most life events as not fully resolved, and therefore not fully integrated in their personal identity and.

Nevertheless, caution must be exercised while interpreting our results due to the small sample size and exclusion of comorbid conditions to select a group with more homogeneous clinical characteristics, and to avoid the effects of concomitant psychiatric disorders. This might have been achieved at the price of generalisability of our results to a wider patient population typically found in clinical practice, where the diagnosis is often accompanied by a psychiatric comorbidity. Furthermore, the absence of another control group comprising patients with DBP but without identity disturbances hampers the ability to draw conclusions specific to this domain of disjunction. Another limitation is inherent to the nature of the disorder characterized by unstable sense of self and a coherent narrative ability. Therefore, patients might be inclined to change their opinions whether events are resolved or not in the week between the administration of the Autobiographical Interview and the scans. In order to minimize the effect of this limitation, participants were asked to read the summaries of life events immediately before the fMRI scans and to confirm that each event was correctly assigned to resolved or unsolved experiences.

The study is innovative in that it focused on a here to fore largely neglected domain of borderline pathology. Using specifically designed autobiographical memory re-enactment task we were able to identify neural underpinning of identity disturbances, which seem to play a key role in the creation of an internal narrative (dlPFC, OFC), awareness of deep emotional states (insula) and mechanisms of mentalization (TPJ). Beyond delineating neural substrates of borderline identity disturbances, our study allows to speculate that recovery from this domain of disfunction is likely to occur under treatment with a focus on integrating divergent or conflicting aspects of the self into a

coherent life narrative. With this in mind, in the following section we set out to investigate the effects of a revised Interpersonal Psychotherapy adapted to Borderline Personality Disorder-Revised (IPT-DBP-R) on brain functioning in attempt to identify the neural mechanism of change mediating recovery from borderline identity disturbances.

5. Post-treatment fMRI study after IPT adapted to DBP-Revised (IPT-BPD-R)

In view of the practical ethos of IPT, its strong theoretical rational and hints from empirical research on factors accounting for variance in treatment outcome, we set out to identify the underlying neural mechanism mediating treatment-induced amelioration in borderline identity disturbances. We propose a revised model of IPT (IPT-DBP-R) [174], based on considerations and minor modifications described in the method section. This is the first fMRI follow-up study using individual and autobiographical stimulus material, aimed at indexing changes of neural activation patterns in response to the recall of individual unresolved life events (ULE) compared to resolved life events (RLE) following 10-month treatment. Given the existing literature, and limited research, we hypothesise that abnormal responses to unresolved versus resolved life events in BPD patients will be normalized after the treatment. Furthermore, we hypothesized that the mechanism of clinical improvement in identity diffusion under the treatment will entail improved regulation of underpinning brain areas identified in our previous research, namely dlPFC, mPFC and the ACC.

5.1. Methods

Methods applied in this follow-up study are similar to those recently published by our research group [151].

Participants

All participants in the study represent a subsample of 19 outpatients with DBP diagnosis from our previous research. Patients in the study were recruited from the Centre for Personality Disorders of the Department of Neuroscience at the University of Turin. We did not find differences between participating and non-participating patients with regard to psychopathology nor with regard to subjective evaluations of RLE and ULE.

19 patients included in the study received a diagnosis of BPD based on DSM-5 criteria [2]. They were matched to a group of 12 healthy subjects for gender, age, and educational attainment (number of years completed at school and university reported by patients and confirmed by school and academic certificates). All DBP patients in our sample had to meet identity disorder as one of the five diagnostic criteria required for diagnosis. Ten patients in the clinical condition were treated with IPT-DBP-R for 10 months, while the other 9 patients were on the waiting list (WL) for the same period of time (mean age of patients IPT-DBP-R ± DS: 36.8 ± 12.5, M / F = 3/7; average age of patients WL ± SD: 37.17 ± 13.23, M / F = 2/7). All had right-handed dominance with range for right handedness Laterality Index (LI) 48 LI < 100 [175].

The exclusion criteria for the clinical group comprised diagnoses of dementia, delirium, and other cognitive disorders; neurological diseases; schizophrenia and other psychotic disorders; bipolar disorders; concurrent major depressive episode; posttraumatic stress disorder, and substance abuse during two months prior to the study. During three weeks before the study, they were free from psychotropic medication and from psychotherapy in the last three months.

Female patients of childbearing age were excluded if they were not using adequate birth control methods (according to the judgment of clinicians). The healthy controls were randomly recruited from general population and assessed using the Structured Clinical Interview for DSM.IV Axis I and II Disorders [176, 177] to control for psychiatric disorders. Another exclusion criterium was a diagnosis of a neurological disorder.

All patients who took part in this trial were evaluated before undergoing fMRI with the following psychometric scales:

- Clinical Global Impression Severity Scale-item (CGI-S) for the assessment of the global severity of symptoms [178];
- Social and Occupational Functioning Assessment Scale (SOFAS) for the assessment of the level of social and professional functioning [179];
- Hamilton scales for depressive and anxious symptoms (HAM-D and HAM-A) [180,181];
- Borderline Personality Disorder Severity Index (BPDSI) for the assessment of

the severity of the specific symptoms of borderline disorder [182];

- Identity Disturbance Questionnaire (IDQ) for the assessment of personal identity disturbances [183];

- Childhood Trauma Questionnaire short version (CTQ) [184] for the evaluation of early traumatic experiences;

- Barratt Impulsiveness Scale-Version 11 (BIS-11) for impulsivity [185];

- Modified Overt Aggression Scale (MOAS) to evaluate aggression [186];

- Self Harm Inventory (SHI) for self-injurious conduct [187].

Participation is the study was voluntary. All participants were fully informed on procedures and objectives of the study, and written informed consent was obtained. The research was conducted in accordance with ethical principles stated in the Declaration of Helsinki guidelines. Approval was obtained from the ethics committee of the University Hospital "Citta della Salute e della Scienza e Ospedale dell'Ordine Mauriziano" of Turin.

Clinical assessments

The clinical assessment was similar to that previously reported [151]. At both times the diagnosis was assessed by an expert clinician and was confirmed using the Structured Clinical Interview for DSM.IV Axis I and II Disorders [161, 162].

Degree of identity integration at both times was assessed using Identity Disturbance Questionnaire (IDQ) [120]. The IDQ is a clinician rated scale comprising 40 items ranging from 1 to 5 (1 ¼ not true at all; 5 ¼ very true) that assesses different manifestations of identity disturbance, including contradictory beliefs and behaviours, changes of values, painful inner incoherence and inconsistency, and confusion over sexual orientation. The scale was developed on the basis of four identity disturbance factors, namely role absorption (in which patients tend to define themselves in terms of a single role or cause), painful incoherence (a subjective sense of lack of coherence), inconsistency (an objective incoherence in thought, feeling, and behaviour), and lack of commitment (to roles or values) [120]. Each item on the scale is associated with one of these four factors, and whilst some items require a degree of inference, other describe relatively manifest aspects of the subject's life.

The score for each factor is obtained with the mean of the related items scores. In our study we used the mean score for the four factors (range values:1-5), with higher scores indicative of a lesser identity integration.

Autobiographical interview

A week before pre-treatment fMRI scanning all participants completed a modified version of the Autobiographical Interview (AI) [122], conducted by an expert clinician (psychiatrist). The interview covered the whole lifespan (childhood, youth, early adulthood, adulthood) and included social relationships, significant others, school, and employment. It yielded 2 unresolved life events and 2 resolved life events. To each event 4 keywords were assigned and subsequently used to trigger active recall during scanning. At the end of the interview the clinician prepared a brief summary for each event (words' number ranged from 25 to 27). As a result, four brief summaries and 16 keywords obtained for each subject comprised the fMRI cue-driven task, used to trigger active recall during scanning. The RLE events were operationalised as processed and settled, whilst the ULE were regarded as not completely integrated in personal life story, and still thus evoking an emotional arousal. In addition, the task comprised four neutral stories identified individually by participants (words' number ranged from 25 to 27) with 4 keywords with a neutral meaning assigned to each. The researchers ensured that neutral stories did not include social content and interpersonal interactions. This was achieved by administering a preliminary set of neutral stories (44) to 130 subjects, who categorized stories and keywords as neutral. Only those found neutral by > 80% of subjects comprised the control condition in the study (21 stories). Prior to post-treatment scanning, subjects were presented with both, life event summary and keywords related to the event to ensure that they were remembered and recalled during image acquisition.

Interpersonal Psychotherapy adapted to DBP-Revised (IPT-DBP-R)

Interpersonal psychotherapy adapted to the borderline patient aims at reshaping personological structure and improve overall functioning. To achieve this, it addresses deficit and conflict in interpersonal relationships, which find expression in symptoms of identity disturbance, feelings of chronic voids, abandonment fears and relational instability.

The adaptation of IPT to DBP by Markowitz [89] has made significant changes to the methods and techniques of classical IPT, initially formulated for depressive disorders. These include a new conceptualization of DBP as a deflected mood disorder similar to dysthymia, but with sporadic outbursts of anger, and the aim to foster mental representations that integrate different aspects of oneself and others. It comprises up to 34 sessions in 8 months, with an acute phase (Phase I) of 18 sessions lasting 50 minutes intended to offer the patient an interpersonal model, establish the therapeutic alliance, limit self-injurious behaviours and obtain an initial clinical improvement. The continuation phase (II phase) comprises 16 sessions and sets out to instil in the patient a more adaptive interpersonal attitudes through the identification and application of new relational strategies, and to reinforce the therapeutic alliance. There is also a telephone contact of 10 minutes a week to manage crises and reduce the risk of drop-outs.

Our research group proposed a revision (IPT-DBP-R) [89] of the Markowitz model, based on below mentioned considerations:

1) Providing more supportive intervention to promote coping with poor compliance and high risk of impulsive conduct;

2) Creating a more flexible model of psychotherapy able to provide more personalized treatments given the complex and heterogeneous clinical pictures that may arise;

3) Extending treatment to allow efficacy studies of IPT-DBT comparing the treatment to other models of psychotherapy (such as DBT or MBT);

4) Increasing the number of sessions and introduction of a maintenance phase in selected cases, given the difficulty of borderline patients to acquire adaptive patterns in interpersonal relationships;

5) Introducing Psychoeducation and Counselling to family members of borderline patients to improve relations with significant others and caregivers.

The proposed IPT-DBP-R is therefore characterised by the following:

1) The first phase of the treatment comprises 22 sessions (20 weeks) and the second phase 20 sessions (20 weeks);

2) Up to two phone calls to the therapist per week;

3) Up to 3 additional sessions in case of problematic treatment completion;

4) Possible two hospitalizations of 7-10 days during psychotherapy. Available ongoing therapy even during hospitalization if the patient's condition allows;

5) Maintenance therapy includes monthly sessions for 8 months in selected patients to reinforce the acquisition of more functional relational modalities

6) An hour of monthly Interpersonal Counselling to 1 or 2 family members for the duration of 6 months.

Stimulus presentation and design

The experiment took place at the Centre of Brain Imaging 3TNIT, at the Hospital Citta della Salute e della Scienza in Turin, Italy. A modified version of the original autobiographical memory recall task was used [138]. A box car design included two activation conditions (ULE and RLE) and a baseline condition (BC), wherein participants were instructed to recall their life events (resolved and unresolved). Activation conditions were presented in a between-subjects randomly balanced order. A summary for each life event was presented to prompt recall. Prior to the task participants were given a computerized training with a set of different events from those utilized during the experimental task. The order of the trial visualization was pseudorandomized using the visual stimuli system E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA) trough specific eyeglasses (Philips Resonance Technology, Inc.).

The fMRI cue-driven paradigm consisted of 24 blocks (8 resolved, 8 unresolved, and 8 neutral). Each block comprised the following: 1) summary, presentation of the brief summary of the event for 15 s; 2) fixation cross for 5/6 s; 3) keyword for 5 s; 4) fixation cross for 6/7 s; 5) response screen for 4s, wherein participants had to classify the emotion they felt as either "positive", "neutral", or "negative" by clicking a button with the first three fingers of the right hand (Figure 1). The purpose of this phase was to ensure that the task was performed correctly. Each block was shown for 45 seconds.

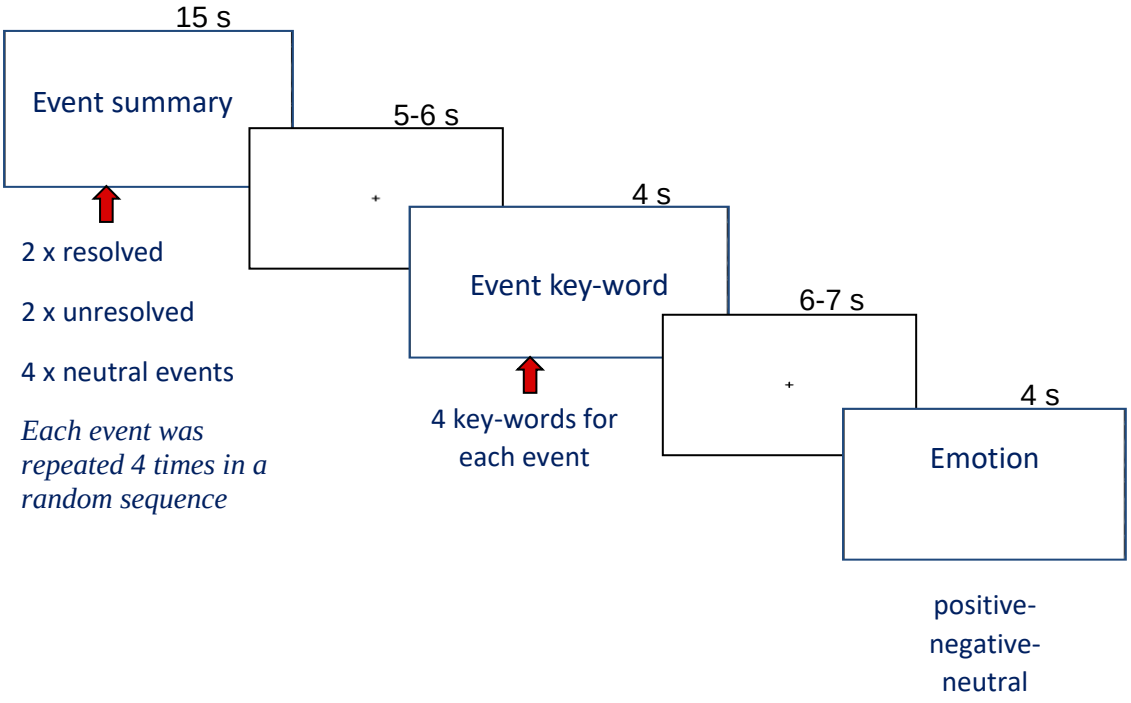


Figure 1. Experimental design. The sequence of presentation of the screens is as follows: "story" screen (15 s); fixation cross (5/6 s); "target word" screen (4 s); fixation cross (6/7 s); "emotion response" screen (4 s), fixation cross (10/12 s).

It is assumed that the life events recalled act as a stimulus for the activity of the brain areas involved in the processes that affect personal identity. The overall duration of this phase was approximately 25 minutes. All subjects underwent pre-and-post-10 months treatment scanning through the application of the same fMRI task and the same experimental procedure. Prior to the post-treatment scan all participants reviewed their event summaries to ensure that they were correctly assigned to resolved, unresolved and neutral category.

MRI acquisition

MRI images were acquired using 3.0 T MRI Scanner (Philips Ingenia) with a 32 channel array head coil. It was equipped with Philips specific eyeglasses (Resonance Tecnology, Inc.). We used an Echo-Planar Image sequence (EPI) (TR/TE ¼ 3000/30 ms, 32 slices, matrix size ¼ 9296, slice gap ¼ 0.5 mm, field of view (FOV) ¼ 224 224 mm^2, flip angle ¼ 90, slices aligned on the AC-PC line during functional run with 415 volumes).

Initial four volumes of run were discarded to allow the equilibration of T1 saturation effects. Structural images of the entire brain were acquired using a T1-weighted sequence (TR 8.1 ms, TI 900 ms, TE 3.7 ms, voxel size 1 1 1 mm^3).

MRI Data Analysis

The functional and structural images were analysed using Statistical Parametric Mapping 8 (SPM8, Welcome Department of Cognitive Neurology, London, UK) [188] implemented in Matlab (Mathworks, Cherborn, MA, USA). All functional images were spatially realigned to the first volume, co-recorded with the average image and segmented in grey matter, white matter and cerebrospinal fluid tissues in anatomical scans, normalized to the Montreal Neurological Institute (MNI) spaced and smoothed with a Gaussian Half-width kernel (FWHM) of maximum 8 mm, with a further levelling of 6 mm on the first level. To remove the low frequency drifts, a high-pass filtering with a cut-off of 128 s was applied. After the pre-processing, the General Linear Model (GLM) was applied to each participant for statistical analysis, by conveying a stick function with a hemodynamic response function (HRF) to the regressors of interest. For each of them, at the first level we calculated and implemented three regressors: resolved keyword, unresolved keyword, neutral keyword. In addition, six parametric regressors without interest in the matrix were included in order to correct the residual effects of head movement. All fMRI data were subjected to rigorous quality controls to exclude movement artefacts (threshold:> 2 mm of translation and 2 degrees of rotation).

At the second level, the SPM 12 software was used in order to explore the neural correlates involved during the recall of resolved and unresolved life events relative to neutral conditions. Initially, for each group separately we performed a one-way within subject ANOVA with a factor (keyword related to the life event) at three levels (solved, unresolved, neutral conditions). Using t-contrasts, resolved, unresolved and neutral conditions were compared. We carried out a complete factorial project with the "group" as an independent between subject factor, and life event factor measured on three levels (resolved keyword, unresolved keyword, neutral keyword).

Linear contrasts have been calculated for the comparison of life events between conditions (resolved keyword, unresolved keyword, neutral keyword): i) resolved event

keyword condition vs neutral event keyword condition and ii) unresolved events keywords condition vs neutral events keyword condition. In light of our thesis on the role of brain networks in the process of autobiographical memories, we defined multiple regions of interest (ROI) a priori and used small volume corrections in these predefined regions, using the mask that includes all the coordinates of interest that emerged from our previous study (151). All of these ROIs were applied for both contrasts: 1. Resolved life event condition vs neutral condition 2. Unresolved life event condition vs neutral condition (the threshold was corrected for the number of ROI: P corrected = 0.05 / 12 = 0.004).

Results

Sample Characteristics

In the treatment group seven patients were females and three were males with age mean ± SD equal to 36.8 ± 12.5. In the waiting list patient group seven were females and two were males with age mean ± SD of 37.17 ± 13.23. The control condition comprised eight females and four males with age mean ± SD equal 36.36 ± 12.85.

Table 1. Post-10 months treatment changes on clinical scales under IPT-DBP-R.

Scales	Treatment	Baseline Mean ± SD	10 months Mean ± SD	Within-subjects effect (duration)	Between-subjects effect (treatment)
CGI-S	IPT-BPD WL	4.00 ± 0.82 4.20 ± 0.79	3.10 ± 0.93 4.08 ± 0.74	0.032	0.009
SOFAS	IPT-BPD WL	57.10 ± 7.06 55.50 ± 9.27	68.22 ± 8.08 57.10 ± 8.73	0.028	0.02
BPDSI	IPT-BPD WL	48.09 ± 5.85 47.45 ± 6.32	36.09 ± 8.57 44.57 ± 6.53	0.001	0.01
BIS-11	IPT-BPD WL	80.22 ± 9.30 81.13 ± 5.96	64.78 ± 12.74 77.37 ± 5.51	0.001	0.031

The analysis was carried out using repeated measures ANOVA upon 10 months IPT-DBP-R treatment completion. The CGI-S scale was used to assess the overall severity of symptoms, the SOFAS scale to index the level of social and occupational functioning, to

assess the severity of specific symptoms of borderline disorder the BPDSI, and BIS- 11 as a measure of impulsivity.

The evaluation was carried out in two stages including pre-treatment (To) and 10 months post-treatment (T_1). In the WL group the evaluation was carried out after 10 months of being on the waiting list. The data were analysed using ANOVA for repeated mixtures having the scales at T_0 and T_1 as repeated measures variable, and the treatment with IPT-DBP-R as a comparison between groups variable.

After 10 months of treatment an improvement in symptoms was evidenced in terms of decreased BPDSI and BIS-11 score, severity of symptoms in terms of decreased CGI-S score, and improved functioning evidenced by increased SOFAS score.

On the level of group comparison, IPT-DBP-R treated patients improved on the CGI-S scales (at baseline 4.00 ± 0.82, after 10 months 3.10 ± 0.93; $\rho = 0.032$) compared to patients on WL (at baseline 4.20 ± 0.79, after 10 months 4.08 ± 0.74; $\rho = 0.032$); SOFAS (at baseline 57.10 ± 7.06, after 10 months 68.22 ± 8.08; $\rho = 0.028$) compared to patients on WL (at baseline 55.50 ± 9.27, after 10 months 57.10 ± 8.73; $\rho = 0.028$); BPDSI (at baseline 48.09 ± 5.85, after 10 months 36.09 ± 8.57; $\rho = 0.001$) compared to patients on WL (at baseline 47.45 ± 6.32, after 10 months 44.57 ± 6.53; $\rho = 0.001$); BIS-11 (at baseline 80.22 ± 9.30, after 10 months 64.78 ± 12.74; $\rho = 0.001$) compared to patients on WL (at baseline 81.13 ± 5.96, after 10 months 77.37 ± 5.51; $\rho = 0.001$). It can therefore be observed that the differences in clinical and functional improvement are marked in the group treated with IPT-DBP-R relative to patients in WL.

The ANOVA analysis for repeated measurements evidenced that the Time factor (Within-subjects duration-effect) was statistically significant regardless of the groups. The effect related to the Group factor (Between-subjects Treatment-effect) was also statistically significant for all scales. Given that the two groups are comparable at T_0, it allows to speculate that the difference between them does not depend on baseline variables, but on the psychotherapy intervention with IPT-DBP-R applied to the target sample. Notably, the significance in the results is greater on specific symptoms of the disorder evidenced by BPDSI and BIS-11 scores compared to the scales that evaluate severity and functioning (CGI-S and SOFAS).

Imaging data

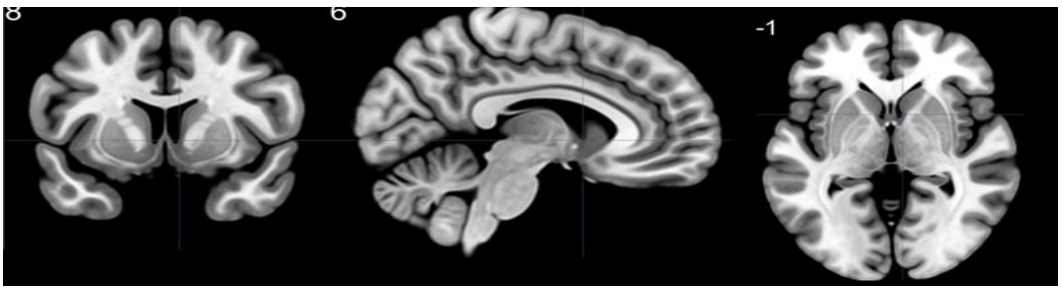
A full factorial between groups analysis on two subgroups of patients with DBP, treated with IPT-DBP-R and patients on WL vs controls revealed significant differences in brain activations in the following t-contrasts: i) keyword of resolved event condition vs neutral keyword ii) unresolved event keywords condition vs neutral keywords condition. Patients with structural abnormalities after fMRI were not excluded from the study.

The obtained results showed that 10 months of IPT-DBP-R had altered activity patterns within rTPJ, rACC and vmPFC in patients with DBP, relative to patients on WL and healthy controls. This downregulation of brain hyperactivity was highlighted during the recall of unresolved life events.

The identified brain areas are involved in self-referential processing, wherein TPJ is a region closely involved in mentalization processes. ACC and vmPFC play an important role in regulating and inhibiting an emotional response in interpersonal contexts.

Regarding the contrasts in the resolved keywords condition vs neutral events, we did not observe difference in brain activity in the right medial prefrontal cortex, in the right anterior cingulate cortex, in the right parietal temporal junction (rTPJ: x = 50; y = 54 ; z = 32) comparing patients with DBP treated with IPT-DBT-R vs patients in WL and healthy controls (Fig.3). This therefore allows to speculate that resolved events are perceived as neutral events in the target patients group vs WL. In other words, the resolved-type events assume the same value on the neural level as the neutral events.

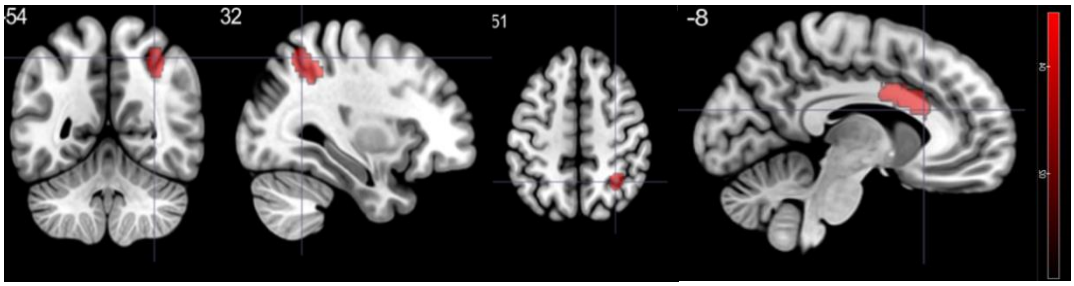
Fig 3. IPT-DBP-R group vs WL during recall of RESOLVED vs neutral events



No difference in brain activity in the right mPFC, right ACC, right TPJ (rTPJ: x = 50; y = 54; z = 32) in IPT-DBT vs WL and HC. RLE assume the same value as the neutral.

With regard to contrasts for the keywords of unresolved condition vs neutral event (Fig. 4), we found significantly less activation in the right medial prefrontal cortex, in the right anterior cingulate cortex and in the right parietal temporal junction (rTPJ: x = 50; y = 54 ; z = 32) in patients with DBP treated with IPT-DBT-R vs patients on WL.

Fig 4. IPT-DBP-R group vs WL during recall of UNSOLVED vs neutral events.



Reduced activity in rTPJ, rACC and vmPFC. These alterations were associated with improved identity integration (IDQ)

Thus, results revealed that the unresolved life events, which in DBP patients are associated with hyperactivity in rTPJ, rACC and mPFC areas, are perceived differently from the neutral events and after psychotherapy are less requited in recall. In addition, we calculated the correlation of brain activity with IDQ scores for the unresolved vs. neutral event condition in each group. The results revealed that improved borderline identity functioning was positively correlated with downregulation of hyperactivity in the target brain areas.

6. Discussion

The current fMRI study was set out to delineate the neural mechanism of symptoms recovery from borderline identity disturbances under Interpersonal Psychotherapy adapted to DBP-Revised (IPT-DBP-R) relative to untreated patients and a group of healthy subjects. In the light of reported literature, it was hypothesized that DBP patients with identity diffusion following a course of psychotherapy with IPT-DBP-R may evidence a downregulation in neural activity patterns in brain areas identified in pre-treatment study compared to untreated borderline subjects and healthy patients.

The level of identity integration in patients and controls was assessed with the IDQ score, which revealed substantial differences between both groups. Our hypothesis was supported by the results, evidencing significant differences in the functioning of specific brain areas in patients with DBP before and after psychotherapy relative to untreated patients and healthy controls. More specifically, significant pre-and post-differences in brain activity patterns in the group of patients involved downregulation in the anterior cingulate cortex, medial prefrontal cortex, and temporal-parietal junction.

Drawing back to pre-treatment data, there was an evidence of hyperactivity in the right ACC and the right mPFC in patients with DBP versus healthy controls during the processing of resolved life events. With regard to unresolved life events, hyperactivity patterns were observed in the bilateral ACC and the right TPJ in patients relative to healthy subjects. Notably, the data revealed an increased activation of ACC in patients with DBP for both resolved and unresolved events, which might be interpreted as an effortful yet ineffective attempt to reconstruct a coherent narrative of significant life events, whether resolved or not. This allows to speculate that patients with DBP might exhibit the tendency to experience most of their life events as not fully processed on the cognitive and emotional level, and therefore poorly integrated within the self- narrative of life experience.

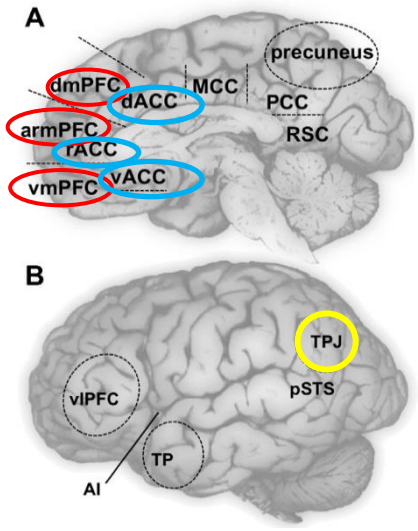
With this in mind, in the post-treatment study we set out to better understand how IPT-DBP-R achieves its therapeutic effects on the level of cerebral reorganisation in the identified areas of insult to the brain. The results revealed that the treatment normalized hyperactivity within the rTPJ, rACC and vmPFC, that are areas involved in self-referential processing and mentalization (Fig.6).

This pattern of brain activity downregulation was evidenced during the processing of unresolved life events, wherein it translates into therapeutic effect on the cognitive and emotional level. Closer examination of the role subserved by these areas will shed critical light on the mechanism of symptomatic recovery from borderline disturbances. It has been found that ACC is the integration point of emotional and attentional aspects of information coming from the body, involved in the modulation of physical and mental pain [136] and the response to adaptational demands [106].

Figure 6.

Figure A shows a medial section of the brain: medial dorsal, anterior rostral and ventral prefrontal cortex (dmPFC, armPFC, vmPFC); anterior ventral, dorsal, rostral and ventral cingulate cortex (dACC, rACC and vACC).

Figure B shows a lateral view of the brain: temporo-parietal junction (TPJ).



It is involved in the identification and evaluation of potentially threatening situations, allowing better emotional and cognitive regulation under stress [82]. ACC has also been found to mediate the attribution of the correct meaning to facial expressions of others [59] and is involved in creating coherent personal narratives [136, 141, 179].It also underpins self-regulation processes, specifically in evaluating the possible advantages of exercising cognitive control in certain situations and in assessing the load of emotional and cognitive resources to be used [13]. Thus, relevant to borderline pathology, ACC hyperactivity is associated with impaired self-reference, negative affectivity and efforts of cognitive control [51]. Normalizing hyperactivity in this area under IPT-DBT-R can therefore act by regulating impulsivity, typically subject to dyscontrol in patients with DBP, promoting the ability to exercise modulation of impulsive and automatic responses. These effects are also likely to benefit borderline identity disturbances, by contributing to forming a more coherent and stable sense of self. Moreover, IPT-DBP-R might improve the mobilization of cognitive and emotional resources necessary to face ambiguous situations in a more adaptive way, and might play a role in common deficit areas, such as the instability of interpersonal relationships, modulation of emotions in interpersonal

contexts, lessening feelings of rejection (hypersensitivity to rejection), abandonment and improved trust towards others.

With regard to other areas of dysfunction, mPFC is involved in the processing of self-related information in both cognitive and emotional motivational aspects that participate the construction of personal identity, such as dreams, aspirations and optimism towards the future [189, 190], in mentalization processes [191] and in regulating and inhibiting emotional response in interpersonal contexts. TPJ is recruited in the ability to recognize own mental states, emotions, intentions and thoughts, and is associated with the theory of mind and mentalization ability [189]. It is also involved in the embodied simulation mechanism carried by mirror neurons [192]. Altered neural activity in mPFC [64, 91] and TPJ [189, 133, 193] in borderline pathology translates into a deficit in awareness of one's emotions and a difficulty in mentalizing the emotional states of others. Treatment with IPT-DBP-R might contribute to increasing awareness of one's emotions, for instance by improving the more purely symptomatic aspects or self-injurious behaviours carried out for self-medication purposes, and to discriminate one's emotional states from those of the others, thereby addressing the more dysfunctional interpersonal aspects. It might also translate into an improvement in socio-occupational functioning of patients, promoting the planning and realization of individual aspirations.

Although six other Pre-and-Post treatment studies have been published regarding borderline pathology, they pertain to the effect of Dialectic Behavioural Therapy on affective regulation and Transference Psychotherapy on impulse control. Moreover, differences in methodology and in the design of experimental tasks to index brain functioning in patients with DBP hamper comparison with the results obtained in other similar studies. Nonetheless, the results of our study are somewhat consistent with those of the first pre- and post-DBT studies despite differences in methodology. Six DBP patients successfully treated with DBT scanned five times before, during and after 12-week hospital treatment program evidenced a decrease in the activity of limbic and cortical areas, including ACC. In another similar study [93] where patients underwent 12 months of digitized DBT with the aim of specifically examining its effect on the regulation of emotions using the DERS scale [194] a preponderant and significant reduction in the overall activation of the amygdala, but not in other areas identified in our

study were reported. This downregulation of brain activity was associated with an improvement in affect regulation.

Two subsequent studies focused on alterations within the neuronal circuits following successful acquisition of strategies useful in the regulation of emotions under DBT. The results of Schmitt *et al*., [156] are in line with those of our study in that a reduction in ACC hyperactivity also emerged after treatment, with greater connectivity of ACC to the prefrontal limbic circuit. Unlike subjects in our study who were outpatients, in this study they were hospitalized and therefore likely to exhibit greater symptoms severity, and receive more intense and supportive care compared to those in our study.

Somewhat similar results were found in another Pre-and-Post DBT study [157] evidencing a reduction in the physiological activity of perigenual ACC and an increased activity in this region during a distraction task in the context of an adverse stimuli. Unlike our study, Winter *et al.,* focused on the degree of emotional vulnerability following a distraction stimulus in borderline patients, thus evaluating the ability of subjects to mobilize more cognitive resources following negative stimuli. After a 12-week treatment with DBT the patients showed greater ability to use the fronto-parietal circuit responsible for regulating emotions and attenuated limbic hyper-reactivity during a distraction task, compared with healthy controls and untreated patients.

Normalizing ACC hyperactivity in neural recovery processes in the regulation of emotions during the perception of pain in patients with DBT was also reported by Niedtfeld *et al.,* [158]. The pre-treatment results revealed an altered connectivity between the left amygdala and dorsal ACC in patients with DBP. This alteration was reduced under 12-week DBT treatment in connection with a normalization of pain processing, and therefore a greater regulation of emotions induced by the therapy.

With regards to the involvement of mPFC in neural recovery processes from borderline disturbances, one study seems to corroborate our results [168], although the objective was specifically the evaluation of affective regulation in borderline patients with self-injurious tendencies. More specifically, it showed that patients who did not complete the DBT cycle evidenced a greater pre-treatment activation in the mPFC, which might reflect a lesser recruitment by the PFC of inhibitory control processes on the impulsive sphere.

This allows to speculate that this pattern of neural activity might be altered under treatment with DBT.

In another study pre-TFP hypoactivation in right dorsal ACC was associated with post-treatment improvements in impulse control [159]. The results of the study are inconsistent with our data and claim that this treatment acts on the regulation of impulsivity, affective instability and aggression inducing an increase in activity in the dorsal prefrontal areas (including dorsal ACC). Unlike ACC and mPFC that are commonly reported in Pre-and-Post treatment studies on neural recovery processes, the effect of psychotherapy on the activity within TPJ is not present in the literature to date.

This finding is therefore innovative and warrant further future studies on the involvement of TPJ in neural recovery processes from borderline identity disturbances. Nonetheless our ability to draw firm conclusions is hampered by some limitations of the current study. The sample size is rather small and comorbid conditions have been excluded to avoid the effects of concomitant psychiatric disorders and to achieve a group with more homogeneous clinical characteristics. This means that this sample is not completely representative of the patients' population with DBP, typically characterized by high symptomatic heterogeneity disguised by the diagnosis. Furthermore, the lack of another control group comprising patients with DBP without identity disturbances means that our ability to draw conclusions specific to borderline self disturbances is also limited.

A further limitation might concern the unstable sense of self and the tendency of patients with DBP to change their opinion regarding significant life events, whether they are resolved or not during the week between the administration of the Autobiographical Interview and magnetic resonance imaging scans. In order to minimize the effect of this limitation participants were asked to read the summaries of life events immediately before the fMRI scans, and to confirm that each event had been correctly assigned to the resolved or unsolved experiences.

The unique contribution of the present study is the evaluation of the effect of IPT-DBT-R on brain functioning in DBP patients with identity disorder under the psychotherapy compared to untreated patients and healthy controls during a recall task of autobiographical memories specifically designed.

To date, this is the first study that has proposed to analyse the effect of this specific type of psychotherapy adapted to DBP. Since identity disturbances are fundamental psychopathological characteristic of borderline pathology, this study represents a further advancement toward matching the most effective therapeutic interventions to the specific pathology profile, thus optimizing the resources available and promoting an improvement of the clinical prognosis. Although the evidence is still preliminary, the results obtained are statistically significant and warrant future efforts to better characterize the neural mechanism behind symptomatic recovery from borderline identity disturbances induced by psychotherapy.

7. Conclusion

Albeit preliminary, our study provides evidence that successful IPT-BPD-R is efficacious in reducing borderline identity disturbances. Moreover, it suggests that the mechanism of neural recovery from self disturbances under IPT-BPD-R entails downregulation of hyperactivity within brain areas mediating social cognition, namely the ACC, mPFC and rTPJ. In light of the existing Pre-and-Post treatment literature on BPD, our fMRI data is the first to highlight alterations within the rTPJ as key processes to achieve therapeutic change in the area of disfunction under study. These findings allow to speculate that IPT-BPD-R therapeutic models is likely to have a specific neural mechanism of action via downregulation of neuronal activity within prefrontal areas, including rACC, mPFC and mainly rTPJ. The rTPJ has been associated with distinct cognitive processes and has been frequently implicated in social cognition tasks, such as perspective taking, empathy, and above all, it has been found to be involved in reorienting of attention and theory of mind. Understanding how our treatment achieves its therapeutic effects on the level of neural functioning does not only advance the empirical status of IPT-BPD-R, but might also contribute to resolving some of the existing controversies over BPD treatment.

Future studies should disentangle key neural processes underlying variety of treatments for which evidence of efficacy has been demonstrated to refine strategies to target specific borderline pathology disguised by the diagnosis.

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