MASARYK UNIVERSITY

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BEHAVIORAL AND NEURAL CHARACTERISTICS AND TARGETED TREATMENTS OF BORDERLINE PERSONALITY DISORDER

Habilitation thesis

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Preface

This habilitation thesis synthesizes the knowledge and experience gained during the past twelve years of my research at the Department of Psychiatry, University Hospital Brno, and the Faculty of Medicine, Masaryk University. The primary focus of my work has been borderline personality disorder (BPD) and the development of targeted interventions for individuals affected by this severe mental disorder. My research has been grounded in the investigation of the behavioral and neural mechanisms underlying the difficulties experienced by these patients. The overarching aim of this thesis is to integrate insights from psychology, psychiatry, and neuroscience with both clinical and research perspectives in order to advance the development of effective, evidence-based treatments and facilitate the translation of research findings into routine clinical practice.

This work would not have been possible without the many individuals who have contributed to our clinical and research endeavors and who have trained, inspired, and supported me throughout my career. I began this journey in 2014 as a Ph.D. student, and I am deeply grateful to my Ph.D. supervisor and long-term mentor, Professor Tomáš Kašpárek, whose guidance helped me develop into an independent researcher. He consistently supported my ideas, encouraged my professional growth, and was always available whenever I needed advice. During my doctoral studies, I established a highly productive collaboration with Professor Christian Schmahl and Dr. Christian Paret from the Central Institute of Mental Health in Mannheim, Germany. Their expertise substantially enriched my understanding of borderline personality disorder and its treatment, and their support played a pivotal role in advancing my research. I would also like to express my sincere gratitude to my clinical supervisor, Amy Essletzbichler Gaglia, who continually inspires me, helps me refine my skills as a dialectical behavior therapist, and is always willing to provide guidance and support during challenging situations.

Over the past years, we have established a research group focused on BPD and conducted several large research projects. I would like to acknowledge my colleagues who worked on our projects, supported our research endeavors and helped shape our work, specifically Martin Lamoš, Jan Širůček, Adéla Látalová, Monika Radimecká, Martin Horký, Patrik Bartys, Eliška Bartečková, Pavel Theiner, Libor Ustohal and Alena Damborská.

In 2019, we established the first comprehensive healthcare-based Dialectical Behavior Therapy (DBT) program in the Czech Republic. Over the past seven years, more than 135 patients have successfully completed the program, and its outcomes are presented in this thesis. I would like to express my sincere gratitude to my colleagues and fellow DBT therapists, whose dedication, expertise, and commitment have been instrumental in providing high-quality care to our patients. In particular, I would like to thank Martin Horký, Irena Komárková, Pavel Theiner, Jan Beránek, Zuzana Špačková, Patrik Bartys, Jana Musálková, Dominika Musilová, Martina Mičková, Adéla Látalová, and Monika Radimecká.

Additionally, many thanks belong to all our patients who have shared their experiences with us and participated in our studies, often despite the considerable time and effort required.

Last but not least, I would like to express my heartfelt gratitude to my husband for his unwavering care, understanding, and support.

Dedicated to the memory of my mom, who supported me throughout my life,
and our beloved cat Sára, who shared my days for eleven years,
both of whom left us shortly before the submission of this thesis.

Summary

Borderline personality disorder (BPD) is a severe mental disorder characterized by pervasive emotion dysregulation, impulsive behavior, unstable interpersonal relationships, identity disturbance, and a high prevalence of self-harming and suicidal behaviors. Despite its substantial burden, targeted forms of effective treatment have only recently become more widely available. This habilitation thesis summarizes twelve years of research focused on the behavioral and neural characteristics of BPD and on the development and implementation of targeted interventions for this patient population.

The first part of the thesis conceptualizes BPD as a disorder of emotion dysregulation and presents research on impulsivity as one of its key behavioral manifestations. The presented studies demonstrate that impulsivity is a multidimensional construct and that emotional impulsivity, particularly negative urgency, plays a central role in BPD. Negative urgency was shown to be associated with clinically significant outcomes, including suicidal behavior and psychiatric hospitalizations. Comparisons with other clinical populations further suggest that impulsivity in BPD is primarily linked to emotional processes rather than to generalized cognitive deficits.

The second part of the thesis focuses on the neural correlates of BPD. Current neuroimaging findings, including studies conducted at our department, support the emotion dysregulation model of BPD and demonstrate alterations in neural systems involved in emotional processing, emotion regulation, social cognition, self-referential thinking, and the consequences of traumatic experiences. These findings provide important implications for the development of targeted interventions.

The final part of the thesis describes several treatment approaches aimed at improving emotion regulation in patients with BPD. Particular attention is devoted to Dialectical Behavior Therapy (DBT), an evidence-based psychotherapeutic treatment that was implemented at our department as the first comprehensive healthcare-based DBT program in the Czech Republic. The thesis further summarizes current knowledge regarding the use of functional magnetic resonance imaging (fMRI) neurofeedback and repetitive transcranial magnetic stimulation (rTMS) as innovative methods for enhancing emotion regulation and reducing symptom severity in BPD.

Overall, the presented findings support the central role of emotion dysregulation in the development and maintenance of BPD and highlight the importance of targeted evidence-based interventions focused on improving emotion regulation abilities. The thesis integrates psychological, psychiatric, and neuroscientific perspectives and demonstrates how research findings can be translated into effective clinical care for patients with BPD.

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List of abbreviations

ADHD – attention-deficit/hyperactivity disorder

BOLD – blood oxygen level dependent

BPD – borderline personality disorder

DBT – dialectical behavior therapy

DLPFC – dorsolateral prefrontal cortex

DMN – default mode network

ECG – electrocardiograph

EEG – electroencephalography

HRV – heart rate variability

ICD – impulse control disorder

fMRI – functional magnetic resonance imaging

MRI – magnetic resonance imaging

PD – Parkinson's disease

pDMN – posterior default mode network

PTSD – post-traumatic stress disorder

rt-fMRI-NF – real-time functional resonance imaging neurofeedback

rTMS – repetitive transcranial magnetic stimulation

TMS – transcranial magnetic stimulation

UPPS-P – impulsive behavior scale (abbrev. for Urgency, lack of Premeditation, lack of Perseverance, Sensation seeking, Positive urgency)

1 Introduction

I began my research on borderline personality disorder (BPD) and emotion dysregulation in 2014 as a Ph.D. student under the supervision of Professor Tomáš Kašpárek at the Department of Psychiatry, University Hospital Brno, and the Faculty of Medicine, Masaryk University. I joined a research project investigating impulsivity in borderline personality disorder (BPD), attention-deficit/hyperactivity disorder (ADHD), and Parkinson's disease (PD). Although impulsive behavior is a common feature of all three disorders, our findings demonstrated that impulsivity manifests differently and is associated with distinct patterns of functional impairment in each condition. This work led to the development of a multidimensional model of impulsivity and a detailed characterization of impulsivity profiles across the three disorders (Hlavatá et al., 2020; Linhartová et al., 2020, 2021).

Subsequently, I contributed to a study of impulsivity in patients with schizophrenia led by Professor Jan Vevera (Juríčková et al., 2023). The findings further underscored the transdiagnostic nature of impulsivity, highlighting that although it represents a common feature across multiple psychiatric disorders, its manifestations and underlying mechanisms vary considerably, necessitating disorder-specific therapeutic approaches.

During my Ph.D. studies, borderline personality disorder (BPD) and emotion dysregulation became my primary research interests. At the same time, I began my clinical practice and developed a strong interest in effective treatments for BPD, which were, at that time, largely unavailable in the Czech Republic. Consistent with the existing literature and theoretical models, our findings demonstrated that impulsive behaviors in BPD, including self-harm and suicidal behaviors, are closely linked to underlying difficulties in emotion regulation (Barteček, Hořínková, Linhartová, & Kašpárek, 2019; Linhartová et al., 2020). Consequently, interventions aimed at strengthening emotion regulation abilities are of central importance in the treatment of patients with BPD. During this period, I regularly attended international conferences focused on BPD, where I met Dr. Christian Paret and Professor Christian Schmahl from the Central Institute of Mental Health in Mannheim, Germany, one of Europe's leading clinical and research centers specializing in BPD. This encounter led to a productive research collaboration that resulted in the implementation of functional magnetic resonance imaging (fMRI) neurofeedback at our institution as an innovative approach to enhancing emotion regulation in patients with BPD (Linhartová, Látalová, et al., 2019), a bilateral mobility grant project and several joint symposium presentations at international conferences.

Most importantly, through this collaboration I became acquainted with Dialectical Behavior Therapy (DBT), one of the most extensively researched and evidence-based treatments for borderline personality disorder. To further develop my expertise, I completed an internship at the Central Institute of Mental Health in Mannheim, including training at its specialized DBT clinic. Subsequently, we assembled a clinical team at the Department of Psychiatry, University Hospital Brno, and underwent intensive training through the British Isles DBT Training Institute. In 2019, we launched the first comprehensive DBT program within the Czech

healthcare system and the second comprehensive DBT program in the Czech Republic overall. Since then, our DBT team has expanded to eleven members, and more than 135 patients with BPD and severe behavioral dysregulation have successfully completed our six-month comprehensive outpatient DBT program.

In addition to providing clinical care, our team has actively contributed to the dissemination and development of DBT in the Czech Republic. In 2023, together with other trained colleagues from across the country, we established the first professional DBT association in the Czech Republic—the DBT Section of the Czech Association for Cognitive Behavioral Therapy. I currently serve as the head of this section.

In 2020, our team was awarded a research grant from the Ministry of Health of the Czech Republic to investigate the behavioral and neural correlates of the effects of our DBT program. As part of this project, we published studies documenting neural differences between patients with BPD and healthy controls (Látalová et al., 2023; Radimecká et al., 2024), and we are currently preparing additional manuscripts evaluating the effectiveness of our DBT program in patients with BPD compared with a clinical control group receiving treatment as usual. Overall, our findings indicate that the program is effective in reducing a broad range of BPD symptoms, including self-harming behaviors. This research has contributed substantially to the implementation and dissemination of DBT in the Czech Republic.

In addition, our team has explored another innovative treatment approach for borderline personality disorder, namely repetitive transcranial magnetic stimulation (rTMS). We conducted a pilot study investigating the effects of high-frequency prefrontal rTMS in patients with BPD, which demonstrated promising efficacy in reducing the severity of BPD symptoms (Tomáš Svěrák et al., 2019). We have also shown that prefrontal rTMS leads to changes in functional brain connectivity in patients with BPD (Svěrák, Linhartová et al., 2022). In 2023, we obtained a research grant from the Ministry of Health of the Czech Republic and conducted a semi-randomized, double-blind, controlled study of prefrontal rTMS in patients with BPD, with a subset of participants simultaneously undergoing the DBT program. The study examines the effectiveness of prefrontal rTMS compared with a sham condition and, furthermore, whether rTMS can be feasibly used as an initial intervention to enhance the effects of psychotherapy. We have thus begun to explore the innovative field of rTMS-augmented psychotherapy, which may further increase the effectiveness of BPD treatment.

At the same time, if prefrontal rTMS proves effective in reducing BPD symptoms, it could become an accessible treatment option for patients awaiting targeted psychotherapeutic interventions such as DBT, as limited availability and long waiting times currently represent major barriers to specialized psychotherapy for BPD in the Czech Republic. This research project has successfully completed the recruitment and assessment phase, and preliminary results were presented at the prestigious Brain Stimulation Congress in 2025 (Horká Linhartová, Bartys, Horký, Radimecká, & Ustohal, 2025; Horký, Bartys, Radimecká, Ustohal, & Horká Linhartová, 2025; Radimecká et al., 2025), and publications arising from this project are currently in preparation and under review in peer-reviewed journals with an impact factor.

This habilitation thesis is conceived as a commentary on published research articles. It begins with an explanation of BPD as a pervasive disorder of emotion regulation (Section 2.1), followed by a description of the multidimensional transdiagnostic model of impulsivity and findings demonstrating the distinct manifestations of impulsivity across different mental and neurological disorders (Sections 2.2 and 2.3). Subsequently, emotion dysregulation is discussed as a key mechanism underlying impulsive behavior in patients with BPD, together with the treatment implications arising from this conceptualization (Section 2.4). Chapter 3 focuses on the neural correlates of BPD and their implications for treatment. Chapter 4 is devoted to targeted interventions for patients with BPD. Specifically, it describes the theoretical background, methodology, and current evidence regarding the effectiveness of Dialectical Behavior Therapy (Section 4.1), fMRI neurofeedback (Section 4.2), and repetitive transcranial magnetic stimulation (rTMS) (Section 4.3). Finally, future directions and emerging needs in BPD research and treatment are discussed in Chapter 5.

Borderline personality disorder (BPD) is a severe mental disorder that can be life-threatening, substantially impairs patients' quality of life, and remains challenging to treat. Moreover, the number of patients with BPD receiving clinical care has increased considerably in recent years. The limited availability of effective treatments contributes to poor clinical outcomes and often leads to frustration and hopelessness among healthcare professionals. In addition, the stigmatization of individuals with BPD remains widespread and can negatively affect treatment engagement and outcomes.

Therefore, the overarching goal of this thesis, as well as of our long-term research and clinical work in this field, is to enhance knowledge and understanding of BPD among both the general public and healthcare professionals, reduce the stigmatization of individuals with BPD, and, most importantly, contribute to the development and dissemination of effective, evidence-based, and targeted treatments for this patient population.

2 Borderline personality disorder in clinical practice

Borderline personality disorder (BPD) is a severe mental disorder characterized by intense and unstable emotions that frequently lead to impulsive and maladaptive behaviors, including substance misuse, disordered eating, and various forms of risk-taking behavior, as well as self-harm and suicidal behavior. The estimated pooled prevalence of BPD is 2.41% in the general population, approximately 12% among psychiatric outpatients, and 22% among psychiatric inpatients (Ramos-Suárez, Guerrero-Jiménez, Cervilla, & Gutiérrez, 2026). BPD is a life-threatening disorder associated with substantial mortality. Meta-analytic estimates indicate a suicide rate of approximately 6%, while an additional 14% of patients die from non-suicidal causes related to the disorder (Lak et al., 2025). BPD also severely decreases the patients' quality of life and limits the ability to participate fully in all life areas, such as school, work,

leisure time, and relationships (ten Have et al., 2016). The number of patients with BPD receiving clinical care has increased considerably in recent years, although the reasons for this trend remain unclear. One contributing factor may be the reduced stigmatization of BPD and improved availability of specialized treatment, which likely facilitate help-seeking and diagnosis. However, these factors alone are unlikely to account for the entire increase. Other potential contributors include heightened peer pressure, social comparison, competitive social environments, social isolation, and sleep disruption, many of which may be amplified by social media use and contribute to increased emotional dysregulation.

Nevertheless, BPD remains a challenging condition to treat, partly because of the frequent occurrence of life-threatening behaviors and partly because the pervasive instability that characterizes the disorder often extends to the treatment process itself. Treatment dropout is common, and many patients repeatedly re-enter the healthcare system during recurrent crises that require medical intervention and/or hospitalization. Moreover, BPD is among the psychiatric disorders associated with the highest levels of stigma, both in the general public and among healthcare professionals (Stiles, Batchelor, Gumley, & Gajwani, 2023). The high level of stigma associated with BPD may be partly attributable to insufficient knowledge and understanding of the disorder, as well as to the limited availability of effective treatments, which often leads to frustration among healthcare professionals, patients, and their families. As a consequence, individuals with BPD are frequently excluded from appropriate care, and some professionals may be reluctant to treat this patient population. Therefore, the development and dissemination of effective, targeted treatments for BPD are of critical importance for both patients and the professionals involved in their care.

The treatment modalities most commonly used in the management of BPD include pharmacotherapy, long-term individual psychotherapy, and hospitalization during periods of acute crisis or when patients present with life-threatening conditions. Regarding pharmacotherapy, patients with BPD are frequently prescribed complex combinations of psychotropic medications, including multiple antidepressants, antipsychotics, mood stabilizers, anticonvulsants, sedatives, and anxiolytics, often at the cost of substantial adverse effects (Tennant, Frampton, Mulder, & Beaglehole, 2023). However, current evidence indicates that no psychotropic medication is effective as a standalone treatment for BPD (Gartlehner et al., 2021; Lieb, Völlm, Rücker, Timmer, & Stoffers, 2010). While some medications may alleviate specific symptoms, they do not reduce the overall severity of the disorder nor address its core feature, namely emotion dysregulation. According to the current American Psychiatric Association guidelines (American Psychiatric Association, 2025), psychotropic medications should be prescribed to patients with BPD only for a time-limited period, with the aim of targeting specific symptoms, and always as an adjunct to psychotherapy. The effectiveness of each medication should be regularly reviewed, and ineffective treatments should be modified or discontinued. Pharmacotherapy should therefore be used cautiously and primarily as symptomatic support.

Moreover, particular caution is warranted because patients with BPD may misuse prescribed medications in suicidal crises (Ning, Theodoros, Harris, & Isoardi, 2023). Consequently, highly lethal medications should be avoided, especially in patients with a history of overdose. Clinicians should also carefully monitor medication availability and prescribe only limited quantities between follow-up appointments. The use of benzodiazepines is generally not recommended, as they may exacerbate emotion dysregulation and are frequently misused by patients with BPD and other disorders characterized by impaired emotion regulation (Albrecht et al., 2014; Colizzi, Meneghin, Bertoldi, & Lugoboni, 2021; Garcia et al., 2000; Tennant et al., 2023).

Hospitalization is often necessary to ensure patient safety during crises associated with a high risk of self-harm or suicidal behavior. However, the duration, frequency, and overall role of hospitalization in the treatment of BPD remain complex and often problematic. Although repeated and prolonged hospitalizations are common among patients with BPD, the nature of the disorder requires patients to learn and practice new emotion regulation and behavioral skills in their everyday environment, something that is impossible or substantially limited during inpatient care (Linehan, 1993). Hospitalization without a targeted therapeutic intervention has not been shown to produce positive outcomes in BPD and may, in some cases, even worsen the patient's condition (Lundahl, Torenfält, Helgesson, & Juth, 2023; Paris, 2004). Evidence of effectiveness is available only for structured inpatient programs specifically designed for the treatment of BPD (Bohus et al., 2004). Furthermore, if hospitalization repeatedly and directly follows episodes of self-harm or suicidal behavior or is extended in direct response to increased suicidal behavior near the planned discharge date, this repeated pattern can inadvertently reinforce maladaptive behaviors. Consequently, recurrent hospitalizations may become counterproductive, often without the awareness of either patients or healthcare professionals.

The clinical challenge is therefore to balance two key principles: ensuring patient safety while minimizing the inadvertent reinforcement of maladaptive behaviors. For patients with BPD, we generally recommend brief stabilization admissions focused on crisis resolution, typically lasting several days and rarely more than a few weeks, ideally before life-threatening behaviors occur. When feasible, a predetermined length of stay is beneficial, with neither early discharge due to improvement nor extension due to worsening symptoms, provided that patient safety allows such an approach. The hospitalization itself should be actively focused on strengthening patients' skills and competencies and preparing them for a successful return to everyday life.

Consequently, psychotherapy represents the only causal treatment that directly addresses the underlying mechanisms of BPD. However, standard forms of psychotherapy are often insufficiently effective for many patients. Individuals with BPD who experience significant behavioral dyscontrol typically require specialized therapeutic approaches. The principal evidence-based psychotherapies for BPD include Mentalization-Based Treatment (MBT), Schema Therapy, Transference-Focused Psychotherapy (TFP), and Dialectical Behavior

Therapy (DBT). As DBT places a strong emphasis on understanding and destigmatizing BPD, the following section presents the disorder from a DBT perspective.

2.1 Borderline personality disorder as pervasive emotion regulation disorder

Dialectical Behavior Therapy (DBT) conceptualizes borderline personality disorder (BPD) as a pervasive disorder of emotion regulation (Linehan, 1993). This conceptualization implies, first, that patients experience emotions that are highly intense, unstable, and rapidly fluctuating. These emotional responses may be triggered by seemingly minor external events or internal processes, such as thoughts, and tend to escalate more quickly, reach greater intensity, and return to baseline more slowly than in healthy individuals. Second, patients have often not acquired effective strategies for managing their emotions and therefore lack adaptive emotion regulation skills. Moreover, emotion dysregulation is associated with a broad range of other symptom domains characteristic of BPD.

One manifestation of emotion dysregulation is an unstable sense of identity and self-esteem. Patients often struggle to describe themselves consistently, may feel like a different person depending on the social context, and frequently change their appearance, hobbies, goals, interests, or life plans. The development of a stable identity is shaped by accumulated experiences regarding what we like and dislike, value and reject, and perceive as pleasant or unpleasant. Because the emotional experiences of patients with BPD are often intense, unstable, and rapidly changing, the development of a coherent and stable sense of self can be significantly impaired. Furthermore, self-esteem and self-worth in individuals with BPD tend to fluctuate markedly in response to their current emotional state. Patients often report feeling like “bad people” and experiencing intense self-hatred, while at other times they may perceive themselves as having few or no significant problems.

Another important symptom domain is interpersonal instability and an intense fear of abandonment. Because patients with BPD often experience emotions much more intensely than most people in comparable situations, their reactions may appear disproportionate to the circumstances and can be difficult for others to understand. For example, when a romantic partner leaves for a weekend business trip, a patient with BPD may experience an intensity of sadness comparable to what most people would feel in response to a permanent loss. As a result, relatively ordinary situations can evoke profound emotional suffering and lead to intense reactions, such as attempts to prevent the partner from leaving. While these reactions are understandable in the context of the patient's emotional experience, they are often ineffective in addressing the situation itself. In addition, patients with BPD may experience rapid shifts in their feelings toward others, alternating between idealization and devaluation, which contributes to instability in interpersonal relationships. Finally, an intense fear of abandonment or loss is common and extends beyond romantic relationships to include friendships, family relationships, and even close attachments to pets.

As mentioned earlier, one of the most serious problems in BPD is impulsive behavior, which includes a wide range of risky and maladaptive behaviors, as well as self-harming and suicidal behavior. These behaviors often occur impulsively during periods of intense emotional distress. Emotions are automatic and complex biological responses that evolved to support survival. Each emotion serves a specific function, is accompanied by characteristic physiological changes, and prepares the individual for particular patterns of behavior. During highly intense emotional states, all humans are more likely to act impulsively in accordance with emotion-driven urges. This mechanism allows for rapid responses in situations where immediate action is required and can, at times, be life-saving. For example, when at a pedestrian crossing and suddenly noticing a rapidly approaching car that does not appear to be slowing down, a person would likely experience intense fear and react immediately by jumping or running out of danger. In such circumstances, acting impulsively on the basis of emotional cues is adaptive and potentially lifesaving. The difficulty for individuals with BPD is that similarly intense emotional reactions are frequently triggered in situations that are not objectively life-threatening. As a result, emotion-driven impulsive behaviors are often ineffective or harmful. From another perspective, many risky and maladaptive behaviors in BPD can be understood as dysfunctional attempts at emotion regulation—strategies that patients have learned to manage overwhelming emotional states while lacking more adaptive and effective means of regulating their emotions.

The final symptom domain in BPD relates to cognitive functioning. One aspect of these difficulties is closely linked to the effects of intense emotions on cognitive processes. During states of extreme emotional arousal, the brain's capacity for higher-order cognitive functioning becomes compromised. Because emotional processing is both faster and evolutionarily prioritized over deliberate thinking, intense emotions can impair attention, memory, learning, and decision-making. This phenomenon is not unique to BPD and can be observed in healthy individuals during highly stressful or emotionally charged situations. However, because patients with BPD experience such intense emotional states more frequently, these cognitive disruptions tend to occur more often and have a greater impact on daily functioning. Additional cognitive difficulties commonly observed in BPD include dissociative experiences, such as derealization and depersonalization. Dissociation can be understood as a coping mechanism through which the brain attempts to protect the individual from overwhelming emotional distress, particularly in situations perceived as inescapable. While dissociative experiences in healthy individuals are typically associated with severe or traumatic events, they may occur relatively frequently in patients with BPD. A major challenge is that effective emotion regulation is difficult during dissociative states; therefore, an important treatment goal is helping patients recognize and interrupt dissociation when it occurs.

2.2 Multidimensional concept of impulsivity

Based on the symptom domains described above, our research has focused on the relationship between impulsivity, emotion, and cognitive functioning. There were two main

reasons for this focus. First, impulsive behaviors in patients with BPD often have serious consequences, including self-harm, suicidal behavior, and other outcomes that can significantly impair quality of life. A better understanding of the factors that influence impulsivity in BPD, and consequently of how patients can improve behavioral control, has the potential to substantially improve patient outcomes and, in some cases, save lives. Second, impulsivity is a transdiagnostic feature observed across a wide range of psychiatric and neurological disorders. However, its manifestations differ considerably between diagnostic groups, suggesting that distinct underlying mechanisms may be involved and that different therapeutic approaches may be required. Therefore, we examined multiple dimensions of impulsivity in three clinical populations—patients with borderline personality disorder (BPD), attention-deficit/hyperactivity disorder (ADHD), and Parkinson's disease (PD)—and compared them with healthy control participants. This project was supported by the Ministry of Health of the Czech Republic (grant no. 15-30062A) and was conducted through a collaboration between University Hospital Brno, the Faculty of Medicine of Masaryk University, and St. Anne's University Hospital Brno.

We assembled a comprehensive assessment battery to examine multiple dimensions of impulsivity based on previous theoretical and empirical findings. The resulting multidimensional model of impulsivity (Linhartová et al., 2021) comprises both self-reported impulsivity, assessed using standardized questionnaires, and behavioral impulsivity, evaluated through computerized behavioral tasks. We included two mostly used self-report measures of impulsivity, namely the Barratt scale (Patton, Stanford, & Barratt, 1995) which is proposed to include three dimensions: motor, attentional, and non-planning impulsivity, and UPPS-P model (Cyders & Smith, 2007; Whiteside & Lynam, 2001) which includes five dimensions: lack of Perseverance, lack of Premeditation, Sensation seeking, and Positive and Negative Urgency, where the last two subscales measure the tendency to act impulsively under positive and negative emotions. Further, we included three behavioral measures of impulsivity. Go/NoGo task (e.g., Wright, Lipszyc, Dupuis, Thayapararajah, & Schachar, 2014) was used to measure the ability to inhibit one's premature or unwanted actions which is also called waiting impulsivity (Robinson et al., 2009). Stop Signal task (Verbruggen & Logan, 2009) was used to measure the ability of stopping one's already ongoing actions which is also called stopping impulsivity (Robinson et al., 2009). Finally, Delay Discounting task (e.g., Richards, Zhang, Mitchell, & de Wit, 1999) was used to measure the preference for immediate rewards at the expense of future consequences and decreased ability to postpone a reward which is also called impulsive choice (Winstanley, Eagle, & Robbins, 2006).

In our initial study (Linhartová et al., 2021; Annex 1), 200 healthy people (54% women, age: M = 23.04, SD = 12.1) underwent the test battery comprised from the Barratt scale, UPPS-P questionnaire, Go/NoGo task, Stop Signal task, and Delay Discounting task. We used confirmatory factor analysis to model the relationships between the individual impulsivity dimensions. As expected, we failed to replicate the factor structure of the Barratt scale similarly to previous studies (Reise, Moore, Sabb, Brown, & London, 2013; Steinberg, Sharp, Stanford,

& Tharp, 2013; Vasconcelos, Malloy-Diniz, & Correa, 2012). On the other hand, our data supported the proposed UPPS-P model with two higher order factors, specifically Deficits in Conscientiousness (comprising from lack of premeditation and lack of perseverance) and Urgency (comprising from negative and positive urgency), while sensation seeking was found to be independent from both the other UPPS-P subscales, and from all other latent variables in the whole model. From these initial findings, we derived a recommendation for preference of UPPS-P questionnaire over the Barratt scale in impulsivity research, and when using the Barratt scale, only use the total score (or test the factor structure before using subscales). In our further studies, we continued to use the UPPS-P questionnaires based on these results. Further, we have included in the model the total Barratt scale score and we excluded from the model the sensation seeking subscale from UPPS-P questionnaire because of its unrelatedness to all other variables.

The final model revealed that the self-report dimensions of impulsivity were largely intercorrelated, which was expected given that they were all assessed using self-report measures. In contrast, the behavioral dimensions were found to be largely independent of one another, possibly reflecting the distinct methodological characteristics of the individual behavioral tasks. Furthermore, we identified two modest associations between self-reported and behavioral dimensions, specifically between urgency and both waiting and stopping impulsivity. These findings suggest that emotional impulsivity is related to the ability to inhibit and stop ongoing actions, even in healthy individuals. Overall, our model demonstrated that impulsivity is a multidimensional construct comprising several largely independent dimensions, and that the observed relationships between these dimensions are strongly influenced by the method of assessment.

2.3 Emotional impulsivity across disorders

In the next part of this project (Linhartová et al., 2020, Annex 2; Hlavatá et al., 2020, Annex 4;), 39 patients with BPD (87% women, age: M = 23.39, SD = 4.82), 25 patients with ADHD (24% women, age: M = 23.28, SD = 8.56), 37 patients with PD (divided in two subgroups: 15 patients with impulse control disorder (ICD; 27% women, age: M = 59.27, SD = 8.88), and 22 patients without ICD (55% women, age: M = 69.18, SD = 5.47)), and 91 healthy controls in total matched for patients by age, gender, and education were administered the impulsivity test battery together with several measures of cognitive functioning. These included namely d2 test measuring attention, digit span test measuring working memory, Tower of London task measuring executive functioning in a neutral context, and Iowa Gambling task measuring executive functioning in an emotional context. We have included the cognitive functioning battery since impairment in cognitive functions can be one of the underlining impairments causing impulsivity, and because all three clinical groups were expected to have a different cognitive profile.

The results showed that both patients with BPD and patients with ADHD exhibited higher levels of impulsivity across all UPPS-P dimensions, with the exception of sensation seeking,

compared with healthy controls (HC). The only UPPS-P dimension that significantly differentiated the two clinical groups was negative urgency, which was substantially higher in patients with BPD than in patients with ADHD, suggesting that it represents a particularly important component of impulsivity in BPD. Further, only patients with ADHD demonstrated increased waiting and stopping impulsivity, as well as impairments in attention, working memory, and emotionally neutral executive functioning, compared with healthy controls. In contrast, patients with BPD did not differ from healthy individuals in these domains. However, both clinical groups exhibited greater impulsive choice and poorer performance in emotional executive functioning relative to healthy controls.

Overall, we observed more widespread impairments in patients with ADHD, including deficits in inhibiting and stopping actions in emotionally neutral contexts, as well as broader impairments in cognitive functioning compared with healthy controls. These findings suggest that impaired cognitive functioning may represent one of the core mechanisms underlying impulsivity in ADHD. In contrast, impulsivity in patients with BPD appeared to be primarily linked to emotional contexts. Patients with BPD exhibited increased impulsivity and cognitive impairments only in tasks involving emotional stimuli or emotionally salient situations. These findings indicate that emotion dysregulation is a key mechanism underlying impulsivity in BPD. This interpretation is further supported by the observation that negative urgency was the most elevated dimension of impulsivity in patients with BPD and was significantly higher than in patients with ADHD.

In our further analysis (Barteček, Hořínková, Linhartová, & Kašpárek, 2019; Annex 3), we found that negative urgency was the only UPPS-P subscale associated with clinically significant indicators of illness severity, including the number of lifetime suicide attempts, lifetime psychiatric hospitalizations, the cumulative number of prescribed psychiatric medications, and the number of aggressive acts during the preceding two years. These findings suggest that negative urgency is closely linked to severe behavioral difficulties and increased healthcare utilization, further highlighting its clinical relevance in patients with BPD.

In case of patients with Parkinson's disease (PD; Hlavatá et al., 2020; Annex 4), we compared two subgroups: those with an impulse control disorder (ICD), defined by the presence of clinically significant impulsive behaviors, and those without ICD. The results showed that patients with PD and ICD exhibited higher levels of lack of perseverance on the UPPS-P scale and higher overall self-reported impulsivity on the Barratt Impulsiveness Scale. However, they performed similarly to patients with PD without ICD and to matched healthy controls on the behavioral measures of impulsivity. Interestingly, in the Iowa Gambling Task, patients with PD and ICD made less risky decisions than both patients without ICD and healthy controls. These findings suggest that performance on standard impulsivity tasks may not necessarily correspond to real-world impulsive behavior in certain clinical populations. More broadly, the results support the notion that the profile and underlying mechanisms of impulsivity can differ substantially across diagnostic groups.

In another project, in which I participated in data analysis and manuscript preparation (Juríčková et al., 2023; Annex 5), impulsivity was examined in patients with schizophrenia who either had or had not exhibited violent behavior. Because aggressive and violent acts are often impulsive in nature, it is important—similarly to self-harming and suicidal behaviors—to determine whether such behaviors are associated with performance on impulsivity measures. Identifying such associations could contribute to improved prediction of the risk of these behaviors in individual patients. The primary measure of impulsivity in this study was the Stop Signal Task, administered using either angry facial expressions (emotional condition) or neutral facial expressions (neutral condition) as stimuli. 117 patients with violent behavior (39,3% women, age: M = 35.77, SD = 9.87), 50 patients without violent behavior (40% women, age: M = 41.8, SD = 11.0) and 50 healthy controls (52% women; age: M = 38.1, SD = 14.9) participated in this study.

The first important result of this study was that 56.41% patients with violent behavior did not complete the task. This dropout rate suggests that behavioral impulsivity tests might be too difficult to finish, especially for highly impulsive patients, which can limit their usage in impulsive patients. The completed data showed that stopping ability was weaker in the emotional condition than in neutral condition in both groups of patients as compared to healthy controls. At the same time, patients who did show violent behavior, had weaker stopping ability in both emotional and neutral context than patients without violent behavior and healthy controls. The results suggest that emotion dysregulation is present in schizophrenia patients in general, and on the other hand, that patients with violent behavior were characterized by higher impulsivity regardless of emotional or neutral context. The study proposes that impulsivity constitutes a higher risk factor for violent behavior in patients with schizophrenia than the disorder itself, and thus confirms the important role of assessing impulsivity in this clinical group. At the same time, the study stresses out the need to develop effective impulsivity tests which even the patients with high impulsivity or severe symptoms such as psychosis will be able and willing to complete.

Annex 1

Linhartová, P., Širůček, J., Ejova, A., Barteček, R., Theiner, P., & Kašpárek, T. (2021). Dimensions of impulsivity in healthy people, patients with borderline personality disorder, and patients with attention-deficit/hyperactivity disorder. *Journal of Attention Disorders*, 25(4), 584–595. doi: 10.1177/1087054718822121

Article

Dimensions of Impulsivity in Healthy People, Patients with Borderline Personality Disorder, and Patients with Attention-Deficit/Hyperactivity Disorder

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Abstract

Objective: Impulsivity, observed in patients with various psychiatric disorders, is a heterogeneous construct with different behavioral manifestations. Through confirmatory factor analysis (CFA), this study tests hypotheses about relationships between dimensions of impulsivity measured using personality questionnaires and behavioral tests. **Method**: The study included 200 healthy people, 40 patients with borderline personality disorder, and 26 patients with attention-deficit/hyperactivity disorder (ADHD) who underwent a comprehensive impulsivity test battery including the Barratt Impulsiveness Scale (BIS), UPPS-P Impulsive Behavior Scale, a Go-NoGo task, a stop-signal task, and a delay discounting task. **Results**: A CFA model comprising three self-reported and three behavioral latent variables reached a good fit. Both patient groups scored higher in the self-reported dimensions and impulsive choice; only the ADHD patients displayed impaired waiting and stopping impulsivity. **Conclusions**: Using the developed CFA model, it is possible to describe relations between impulsivity dimensions and show different impulsivity patterns in patient populations. *(J. of Att. Dis. 2021; 25(4) 584-595)*

Keywords

impulsivity, confirmatory factor analysis, latent factor model, borderline personality disorder, ADHD

Introduction

Impulsivity can be broadly defined as the degree to which one tends to act on the spur of the moment without considering consequences. Impulsive behaviors have been theorized to include substance abuse, gambling, dangerous sexual behavior, risky driving, binge eating, aggression, self-harm, and suicidality (Barteček, Hořínková, Linhartová, & Kašpárek, 2019; Cyders, Combs, Fried, Zapolski, & Smith, 2009). Heightened impulsivity has been identified as a diagnostic feature of borderline personality disorder (BPD) and attention-deficit/hyperactivity disorder (ADHD) by diagnostic manuals (American Psychiatric Association [APA], 2013; World Health Organization, 2011), but it has also been observed in patients with many other psychiatric conditions, including addiction (Smith, Mattick, Jamadar, & Iredale, 2014), bipolar disorder (Najt et al., 2007), and schizophrenia (Ouzir, 2013).

Although existing literature clearly indicates that there is no global impulsivity factor (MacKillop et al., 2014; MacKillop et al., 2016; Stahl et al., 2014), there remains uncertainty about what the dimensions of impulsivity are and how they relate to each other. Existing classifications of impulsivity dimensions have followed one of two broad approaches. Under the more traditional approach, impulsivity is considered a personality trait, extremely high levels of which can have pathological consequences. Dimensions of impulsivity are then measured by self-report questionnaires and identified through factor analysis. According to the other view, impulsivity results from the disruption of specific cognitive abilities, such as the ability to postpone or interrupt actions. Behavioral tests of various impulsivity-related cognitive abilities have been developed to measure separate impulsivity dimensions. However, there has been little empirical investigation into whether these dimensions are truly independent (as in MacKillop et al., 2016; Stahl et al., 2014). Furthermore, investigations of the relationships between personality-based and behavioral dimensions have been rare (e.g., Cyders & Coskunpinar, 2011; MacKillop

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et al., 2016). Thus, our aim, following a review of proposed impulsivity dimensions, is to conduct a confirmatory factor analysis (CFA), examining relationships between personality-based and behavioral dimensions of impulsivity. After specifying a well-fitting CFA model, we can examine (a) whether people with impulsivity-related psychiatric conditions (BPD and ADHD in the current study) exhibit higher levels of certain dimensions, and (b) whether the two patient groups differ from each other in their impulsivity profiles.

Personality Models of Impulsivity

Of the theories according to which impulsivity is a personality trait (for historical reviews, see Evenden, 1999; Parker & Bagby, 1997), the most dominant models are represented by the Barratt Scale (BIS, Barratt, 1959) and the UPPS-P Scale (Cyders & Smith, 2007; Whiteside & Lynam, 2001). The eleventh version of BIS (Patton, Stanford, & Barratt, 1995) has been in use for more than 20 years. Through factor analysis, the scale's authors found that the items reflected three main dimensions: attentional, motor, and nonplanning impulsivity. However, most subsequent studies have failed to replicate this three-factor structure and to uncover one global factor (e.g., Reise, Moore, Sabb, Brown, & London, 2013; Steinberg, Sharp, Stanford, & Tharp, 2013; Vasconcelos, Malloy-Diniz, & Correa, 2012), although it is common for researchers and clinicians to calculate the total BIS score. Regardless of its limitations, the BIS remains widely used and has been found to differentiate between healthy people and patients with impulsivity-related disorders (Stanford et al., 2009), including BPD (e.g., Barker et al., 2015; Maraz et al., 2016) and ADHD (e.g., Chamberlain, Ioannidis, Leppink, & Niaz, 2017; Roberts, Milich, & Fillmore, 2016).

The UPPS-P personality model of impulsivity (Cyders & Smith, 2007; Whiteside & Lynam, 2001) was developed in an effort to integrate a number of proposed personality models. Whiteside and Lynam (2001) developed a scale that included 20 subscales from nine existing questionnaires and 14 original items. Factor analysis revealed four impulsivity factors: urgency (U), (lack of) perseverance (P), (lack of) premeditation (P), and sensation seeking (S). Subsequently, Cyders and Smith (2007) developed a revised scale, the UPPS-P, which contained an additional urgency subscale gauging impulsive behavior under the influence of positive emotions. A CFA of the UPPS-P conducted by these authors revealed a hierarchical structure in which negative and positive urgency reflected a higher-order "urgency" factor, while lack of perseverance and premeditation reflected higher-order "deficits in conscientiousness." Sensation seeking was found to be a separate factor. In introducing the notion of urgency—a tendency to act impulsively under influence of emotions—the UPPS-P took into account emotional impulsivity, which had been previously overlooked. Numerous studies showed each of the lower order factors to be associated with various forms of psychopathology (Berg, Latzman, Bliwise, & Lilienfeld, 2015). Compared to healthy people, heightened scores on all UPPS-P subscales except sensation seeking were observed among both BPD patients (e.g., Bøen et al., 2015; Paret, Hoesterey, Kleindienst, & Schmahl, 2016) and ADHD patients (e.g., Lopez, Dauvilliers, Jaussent, Billieux, & Bayard, 2015; Pedersen et al., 2016).

Behavioral Models of Impulsivity

Behavioral models of impulsivity can be divided into two broad subtypes (i.e., dimensions). Each behavioral impulsivity subtype can be assessed through several behavioral tests, summarized in Figure 1. The figure also summarizes other labels used for these dimensions in the literature.

The first subtype, which we will call "impulsive action" (Winstanley, Eagle, & Robbins, 2006), involves impaired inhibition with respect to withholding premature actions or stopping ongoing actions. In effect, impulsive action can be subdivided into "waiting impulsivity" (difficulty inhibiting or postponing unwanted or premature actions) and "stopping impulsivity" (difficulty interrupting already ongoing actions; Robinson et al., 2009). The most frequently used test for measuring waiting impulsivity is the Go-NoGo task (GNG; e.g., Smith et al., 2014). BPD patients usually show no impairment in GNG (Hagenhoff et al., 2013; van Eijk et al., 2015), but their performance has been shown to decrease under the influence of emotions (Krause-Utz et al., 2016; Turner, Sebastian, & Tüscher, 2017). The examination of ADHD patients' performance in the GNG has produced mixed results (Pani et al., 2013; Rubia, Smith, & Taylor, 2007; Schachar et al., 2007), possibly because of the influence of task parameters on GNG performance (Metin, Roeyers, Wiersema, Van Der Meere, & Sonuga-Barke, 2012; Nieuwenhuis, Yeung, van den Wildenberg, & Ridderinkhof, 2003). Stopping impulsivity is typically measured using the stop-signal task (SST; Verbruggen & Logan, 2009). BPD patients usually manifest no deficits in SST (Barker et al., 2015; Jacob et al., 2010), whereas ADHD patients usually do show impairment (Lampe et al., 2007; Pani et al., 2013).

The second impulsivity subtype, which we will call "impulsive choice" (Winstanley et al., 2006), involves impaired decision making. People with high levels of impulsive choice prefer immediate gains or rewards at the expense of future goals. For these individuals, the value of a reward drops rapidly if they must wait for it. The most frequently used test for measuring impulsive choice is the delay discounting task (DDT; Ainslie, 1975). Both BPD and ADHD patients continuously show higher levels of discounting, implying more pronounced impulsive choice (Barker et al., 2015; Patros et al., 2016; Turner et al., 2017).

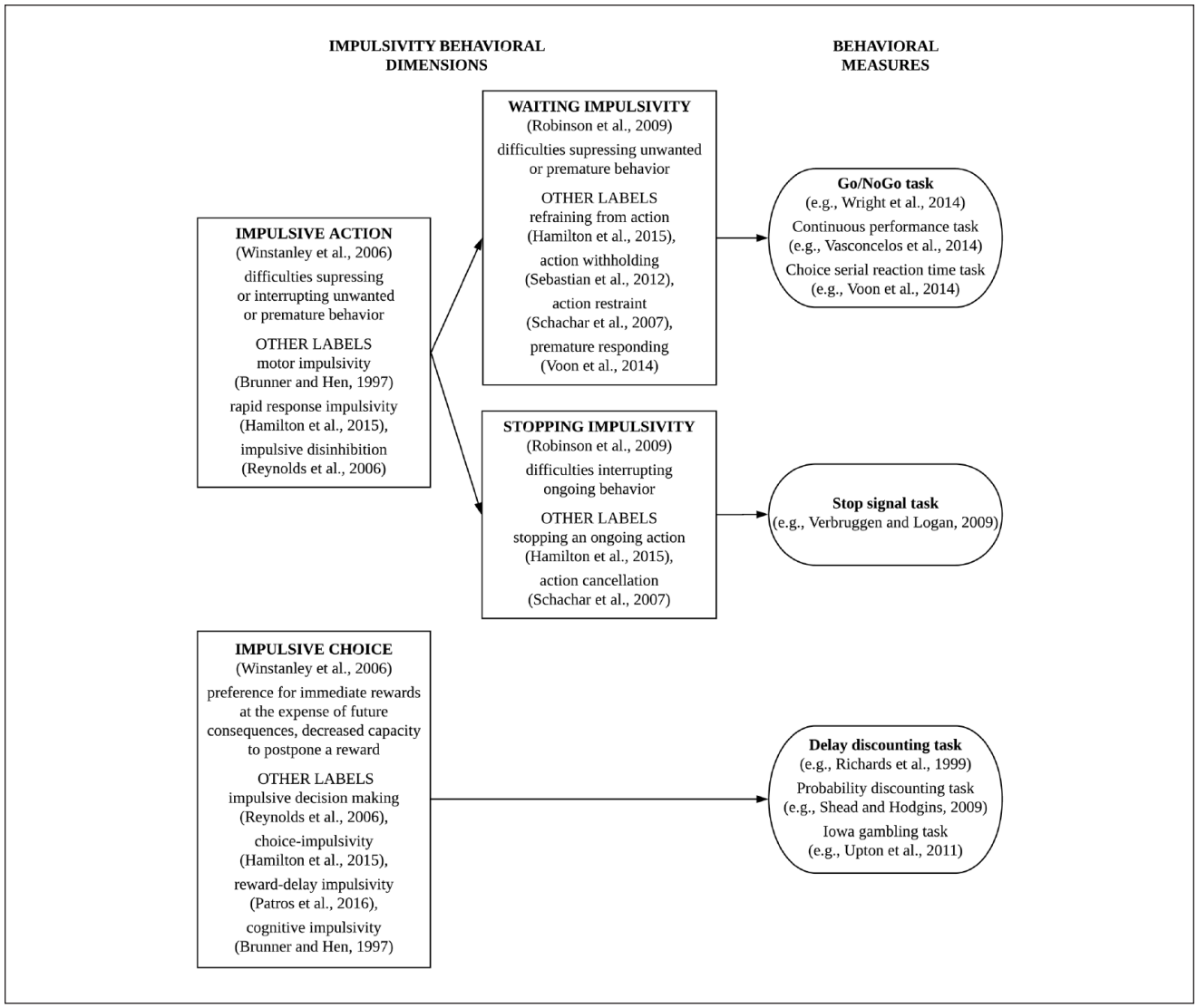

Figure 1. Overview of the behavioral impulsivity dimensions based on existing literature.
Note. In the rightmost column describing measures, the main test employed for measuring the associated construct is in bold, with alternative tests being named underneath.

Relationships Between Impulsivity Subtypes

The impulsivity dimensions of the BIS and the UPPS-P have generally been found to be related (e.g., Lozano, 2015; MacKillop et al., 2016). Within the UPPS-P itself, studies looking at relationships between higher-order factors (Cyders & Smith, 2007; Linhartová et al., 2017) have found moderate-to-high correlations between deficits in conscientiousness and urgency. Sensation seeking has, meanwhile, been found to have moderate-to-no relationship with the two other factors.

Regarding the behavioral dimensions, there is evidence from neuroimaging studies that waiting and stopping impulsivity are two different processes (Eagle, Bari, & Robbins, 2008; Swick, Ashley, & Turken, 2011). In line with this finding, patients with the same psychiatric disorder have been found to perform differently in GNG than in SST (Pani et al., 2013; Smith et al., 2014). Despite these findings, most studies either do not report correlations between GNG and SST or model the tests as measures of one impulsive action dimension (MacKillop et al., 2016; Stahl et al., 2014), so little is known about the strength of the relationship between waiting and stopping impulsivity. Impulsive action, modeled as a latent variable reflecting waiting and stopping impulsivity, has, meanwhile, been repeatedly found to be independent from impulsive choice (MacKillop et al., 2016; Stahl et al., 2014).

The relationship between different personality and behavioral dimensions has received little research attention. A

recent study using CFA found a low but statistically significant association between a latent factor defined by the UPPS-P and the BIS subscales and impulsive choice, as well as impulsive action (MacKillop et al., 2016). However, in collapsing all personality dimensions into one latent factor and doing the same for waiting and stopping impulsivity, this approach prevents us from drawing hypotheses about relationships between potentially distinct personality and behavioral impulsivity dimensions. Earlier, Cyders and Coskunpinar (2011) performed a meta-analysis of 28 studies presenting correlations between different impulsivity personality and behavioral measures. The authors found a significant but very small general association between personality and behavioral measures ($r = 0.10$). Specific results are difficult to interpret because the authors collapsed different measures into predefined categories which were consequently compared. Generally, the degree of overlap between personality and behavioral impulsivity measures found in existing studies is very low.

Current Study: Aims and Hypotheses

Our overarching hypothesis is that the BIS, deficits in conscientiousness, urgency, sensation seeking, waiting impulsivity (measured by GNG), stopping impulsivity (measured by SST), and impulsive choice (measured by DDT) constitute separate dimensions of impulsivity either in that they have only weak-to-moderate interrelationships as latent variables within the CFA model, or in that, as latent variables, they differ in clinical profile—that is, in how they differentiate among healthy people, patients with BPD, and patients with ADHD. We do not incorporate a higher-order impulsive action latent variable composed of waiting and stopping impulsivity, so that both dimensions can be interpreted separately. Similarly, we do not hypothesize any higher-order latent variables defined by two or more personality latent variables.

With respect to the interrelationships of dimensions, one hypothesis is that deficits in conscientiousness, urgency, and the BIS will be intercorrelated or have similar clinical profiles, while sensation seeking will be independent of these factors in terms of correlations and clinical profiles. We also hypothesize weak-to-no intercorrelations between the personality dimensions (BIS, deficits in conscientiousness, urgency, and sensation seeking) and the behavioral dimensions (waiting impulsivity, stopping impulsivity and impulsive choice). There is insufficient data to make a hypothesis about the relationship between waiting and stopping impulsivity. However, there is a basis for hypothesizing that both BPD and ADHD patients will differ from healthy controls in impulsive choice and on all self-report dimensions except sensation seeking. We further hypothesize that ADHD patients differ from healthy controls in stopping impulsivity; considering the inconsistencies in the literature, we make no hypothesis about the difference between ADHD patients and healthy controls in waiting impulsivity.

Method

This study was reviewed and approved by the Institutional Ethical Committee. Before the research was carried out, the study was explained thoroughly to the subjects who then signed informed consent forms. The research was carried out in accordance with APA ethical standards.

Participants

The participant pool consisted of 200 healthy people (54% women, age: $M = 23.04$, $SD = 12.1$), 40 patients with BPD (88% women, age: $M = 23.40$, $SD = 4.72$), and 26 patients with ADHD (31% women, age: $M = 26.15$, $SD = 12.77$). The ADHD diagnosis was confirmed by two board-certified psychiatrists according to *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*; APA, 2013) and the Diagnostic Interview for ADHD in adults (DIVA; Kooij, 2012). The BPD diagnosis was confirmed by two board-certified psychiatrists according to *DSM-V* criteria and by a psychologist using the Diagnostic Interview for Borderlines, revised (DIB-R; Zanarini, Gunderson, Frankenburg, & Chauncey, 1989). Comorbid psychotic or affective disorder and addiction were the exclusion criteria. The Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) was conducted with healthy volunteers to confirm the absence of psychiatric symptoms. 40 people (88% women, age: $M = 24.25$, $SD = 6.88$) from the healthy sample were matched to BPD patients on age, gender, and education; a further 26 (31% of women, age: 24.46, $SD = 7.94$) were similarly matched to ADHD patients.

Procedure

Under the supervision of a research assistant, participants completed a single 60-min test battery comprising two questionnaires and three computerized behavioral tests. The tests were presented in a fixed order.

Measures

Validated translations of the Barratt Scale (BIS, 11th version, 30 items, Patton et al., 1995) and the UPPS-P scale (Cyders & Smith, 2007) were used (Linhartová et al., 2017). The UPPS-P consisted of five subscales: lack of premeditation (11 items), lack of perseverance (10 items), sensation seeking (12 items), negative urgency (12 items), and positive urgency (14 items). Behavioral measures were developed in E-Prime 2.0. Waiting impulsivity was measured by a GNG task, stopping impulsivity by an SST, and impulsive choice by a DDT.

The GNG used white letters A and B on a black background as stimuli. Participants were asked to press the space key on the computer keyboard whenever a Go stimulus (the letter "A") appeared and to suppress that action whenever a NoGo stimulus (the letter "B") appeared. Go stimuli were highly prevalent (83%) to make action suppression less automatic and thus encourage more NoGo commissions (Nieuwenhuis et al., 2003). Stimuli duration was 0.4 s; each stimulus was preceded by a fixation cross with variable duration between 1.1 s and 2.6 s. The whole task included four blocks with 48 trials in each block. Two accuracy-based and two reaction-time-based indices were derived from the GNG, namely *NoGo commissions percentage* (percentage of NoGo trials erroneously followed by a key press), *Go omissions percentage* (percentage of Go trials erroneously followed by no key press), *NoGo reaction time* (average reaction time on erroneous NoGo trials) and *Go reaction time* (average reaction time on correct Go trials).

The SST used white left and right arrows on a black background as the Go stimuli. Participants were asked to press the left or right arrow key when the respective Go stimulus appeared, except when the Go stimulus was followed by a stop signal: a change in the arrow color from white to red. The time between the Go stimulus and the appearance of the stop signal—the stop-signal delay (SSD)—was initially set to 200 ms and decreased by 45 ms whenever action suppression was successful, while increasing by 45 ms after unsuccessful Stop trials (Verbruggen & Logan, 2009). Stop-signal frequency was 25%; each trial ended either after the participant's response or, in the absence of a response, 1 s after the appearance of the stimulus. Each trial was preceded by a fixation cross with a variable duration between 1.1 s and 2.6 s. The whole task included four blocks with 48 trials in each block. Three accuracy-based indices were derived from the SST, namely *Stop commissions percentage* (percentage of Stop trials erroneously followed by a key press), *Go commissions percentage* (percentage of left [right] arrow Go trials erroneously followed by right [left] arrow key press), *Go omissions percentage* (percentage of Go trials erroneously followed by no key press). The two reaction-time-based indices derived from the SST include *Go reaction time* (average reaction time on correct Go trials) and *stop-signal reaction time* (*SSRT*) which was estimated by subtracting the average SSD from the average Go reaction time. The SSRT provides an indication of the average time required for successful stopping. Longer SSRTs indicate greater difficulty interrupting actions.

In the DDT, participants were asked to answer a set of questions requiring a choice between a smaller but immediate reward (IR) and a higher but delayed reward (DR; e.g., *Would you rather receive 510 CZK now, or 990 CZK in a month?*). For each combination of a DR amount and a delay period (D), different immediate reward amounts were displayed until an "indifference point" (IP) could be determined for the combination. The IP is the immediate reward amount that has the same subjective value as the higher delayed reward. Questions regarding different IRs and DRs were presented in random order, with the IR being selected according to the procedure described by Richards, Zhang, Mitchell, and de Wit (1999). The Ds and DRs were determined based on pilot studies. Chosen Ds were 1 day, 1 week, 1 month, 3 months, and 6 months. Two DRs were chosen: a smaller amount of 990 CZK (approx. 40 EUR), and a higher amount approximately equivalent to the median monthly salary in the Czech Republic (24.900 CZK, approx. 980 EUR). The IR amounts varied in 20 CZK steps in questions about the smaller DR and in 500 CZK steps in questions about the higher DR.

Two indices (*k parameter and Area Under the Curve*) were derived for each DR, resulting into four DDT indices. Based on the IPs for each DR, each participant's "discounting parameter," k, was estimated using the following hyperbolic function, across multiple Ds on the x-axis and a fixed DR amount: $DR = IR / (1 + k \times D)$. Higher values of k indicate steeper (i.e., quicker) discounting with increased delay, and, correspondingly, higher levels of impulsive choice (Mazur, 1987). The Area Under the Curve (*AUC*) in the DDT graph, was derived by connecting the IPs for multiple Ds (Myerson, Green, & Warusawitharana, 2001). The higher the AUC, the slower the discounting, and the higher the impulsive choice. The advantage of the AUC is in its independence from the theoretical discounting function used to derive k.

Statistical Analysis

The CFA model (presented in Figure 2) was estimated using the *lavaan* package (Rosseel, 2012) in *R* (v. 3.5.1). Robust maximum likelihood (RML) based on a full-information matrix likelihood (FIML) was used as the estimation method. The latent variables were (a) the BIS, (b) deficits in conscientiousness (lack of premeditation and lack of perseverance subscales from the UPPS-P), (c) urgency (negative urgency and positive urgency subscales from the UPPS-P), (d) sensation seeking (from the UPPS-P), (e) waiting impulsivity as measured by GNG, (f) stopping impulsivity as measured by SST, and (g) impulsive choice as measured by DDT. All correlations between latent variables were allowed.

The observed variables defining the personality dimensions (1-4) were determined based on preliminary CFAs, conducted separately for the BIS and the UPPS-P. As expected, for the BIS, we failed to find an adequate model fit for the proposed three-factor structure[1] or unidimensional solution.[2] However, because of its ability to discriminate between healthy people and some clinical populations, the scale was retained in the main model and was represented as a single latent factor, defined by two parcels

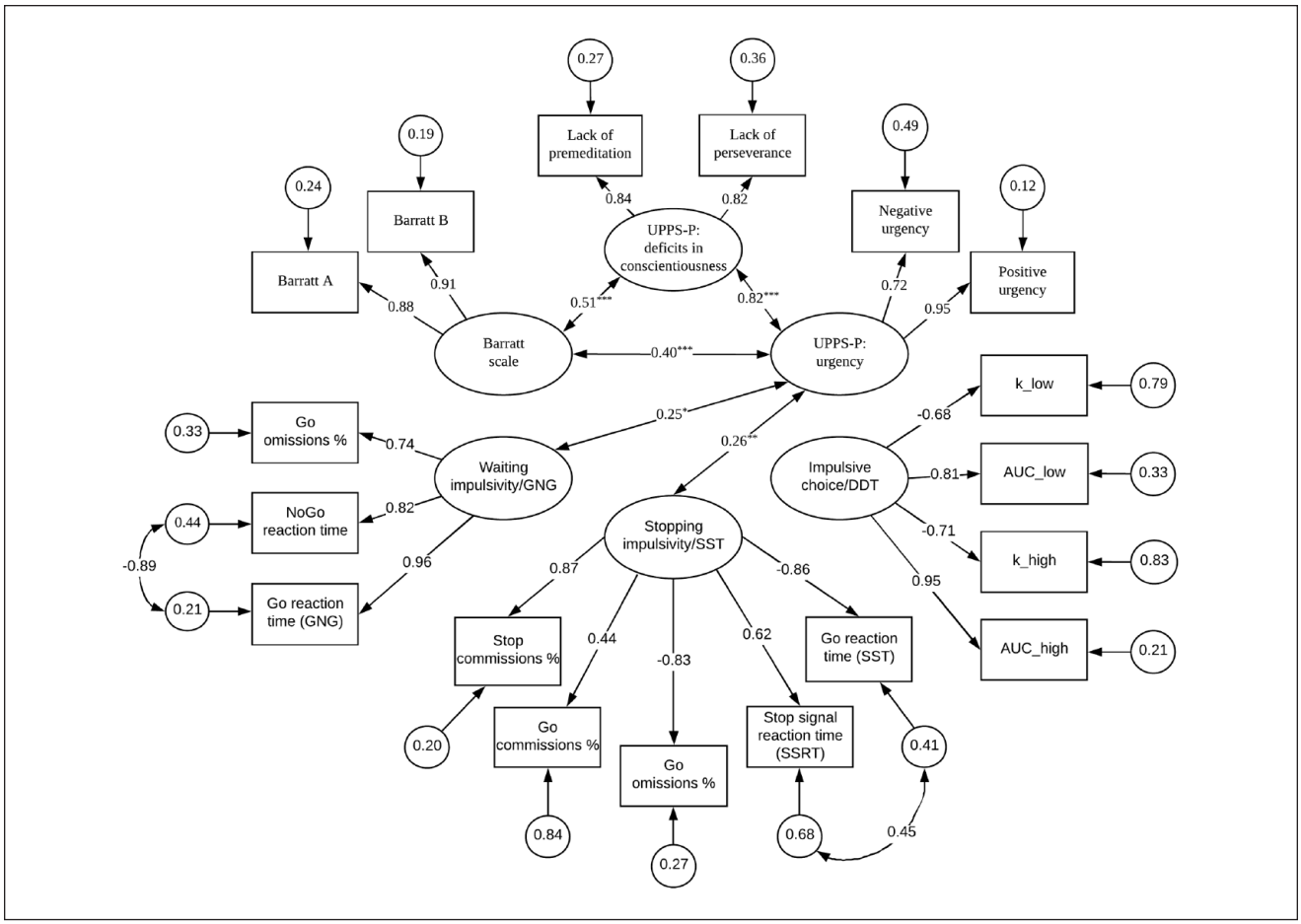

Figure 2. Estimated latent factor model of impulsivity dimensions.

Note. All coefficients are presented standardized. For clarity, only correlations higher than 0.2 between latent variables are presented in this figure. All correlations between latent variables are presented in Table 2. GNG = Go-NoGo task; SST = stop-signal task; DDT = delay discounting task; AUC = area under the curve. UPPS-P is an acronym based on method subscales (Urgency, Premeditation, Perseverance, Sensation seeking, Positive urgency). *$p < .05$. **$p < .01$. ***$p < .001$.

(randomly selected half of the items in each parcel) with regression parameters constrained to be equal (Little, Cunningham, Shahar, & Widaman, 2002). In the preliminary CFA of UPPS-P items, in line with earlier findings we found a well-fitting model comprising three latent variables: deficits in conscientiousness (defined by lack of perseverance and lack of premeditation subscales), urgency (defined by the negative urgency and positive urgency subscales) and sensation seeking (defined by three item parcels).[3] Urgency correlated strongly ($r = 0.71$) with deficits in conscientiousness, while sensation seeking was independent of the other higher-order latent factors.

The observed variables defining the behavioral dimensions (5-7) are described in Method section. There are two types of indices from the GNG and SST: accuracy-based and reaction-time-based. Similarly to Stahl et al. (2014), we argue that task performance is characterized by a combination of these indices, not only by a single predefined variable. To reduce model complexity (and avoid a Heywood case), an equality constraint was placed on the regression parameters of the relationship between the waiting impulsivity/GNG latent variable and NoGo reaction time and Go reaction time. Furthermore, residual correlations between SSRT and Go reaction time in SST and between NoGo reaction time and Go reaction time in GNG were allowed, so that individual differences in reaction times were not overestimated. After model-fitting to the full healthy sample, latent scores for BPD patients, ADHD patients, and matched healthy controls were estimated and compared between the matched groups.

Results

The correlation matrix of all observed variables is provided in Supplemental material. The model described in the previous section showed a not-quite-sufficient robust fit, $\chi^2 = 413.634$; $df = 190$; $\chi^2/df = 2.177$; comparative fit index (CFI) = 0.867,

Table 1. Mean Differences in Latent Variable Scores Between Patients With BPD ($N = 40$) and Their Matched Healthy Controls ($N = 40$), and Between Patients With ADHD ($N = 26$) and Their Matched Healthy Controls ($N = 26$).

	BPD			ADHD		
Latent variable	$t(78)$	p	Cohen's d	$t(50)$	p	Cohen's d
Barratt Scale	−8.00	<.001	−1.79	−6.42	<.001	−1.78
Deficits in conscientiousness	−6.68	<.001	−1.49	−4.17	<.001	−1.16
Urgency	−8.55	<.001	−1.91	−6.49	<.001	−1.80
Waiting impulsivity/GNG	−0.71	.479	−0.16	−2.78	.008	−0.77
Stopping impulsivity/SST	−1.16	.250	−0.26	−2.37	.022	−0.66
Impulsive choice/DDT	4.99	<.001	1.12	3.72	<.001	1.03

Note. Group assignment: 0 = controls, 1 = patients; negative differences indicate higher values in patients than in healthy controls in all variables. Higher values in patients than in healthy controls indicate higher impulsivity in patients in all variables except Impulsive choice/DDT. In Impulsive choice/DDT, lower values in patients than in healthy controls indicate higher impulsivity in patients because the latent variable's valence is driven by AUC observed variables (see Method for AUC index computation). BPD = borderline personality disorder; GNG = Go-NoGo task; SST = stop-signal task; DDT = delay discounting task; AUC = Area under the Curve.

root mean square error approximation (RMSEA) = 0.075; standardized root mean square residual (SRMR) = 0.079. Two changes were made to the initial model. First, sensation seeking was removed from the model, as it was (a) completely independent of all the other latent variables, and (b) in exploratory analyses, no different across patients and matched controls. Second, NoGo commissions—an observed variable loading on the waiting impulsivity/GNG latent variable—was removed from the model, as it had too low associated regression coefficient (0.22). The updated model is presented in Figure 2 and obtained a good robust fit ($\chi^2 = 226.204$; $df = 122$; $\chi^2/df = 1.854$; CFI = 0.921, RMSEA = 0.065; SRMR = 0.067). Following model specifications among healthy participants, latent variable scores were estimated for BPD patients, ADHD patients, and matched controls. The results of t tests comparing matched groups are presented in Table 1.

In line with our hypothesis of intercorrelations for deficits in conscientiousness, urgency, and the BIS, we observed a strong and significant correlation ($r = 0.82$) between deficits in conscientiousness and urgency. Moreover, both deficits in conscientiousness and urgency were moderately and significantly correlated with the BIS ($r = 0.51$ and 0.40), and BPD patients and ADHD patients scored higher than matched controls on all three latent variables. With respect to our hypothesis of small-to-no correlations between the self-report-based dimensions and the behavioral dimensions, we observed two significant low correlations of urgency with waiting impulsivity/GNG ($r = 0.25$) and stopping impulsivity/SST ($r = 0.26$). Furthermore, two very low marginally significant correlations ($r < 0.02$) were found between BIS and impulsive choice/DDT, and between deficits in conscientiousness and stopping impulsivity/SST. No hypothesis was made regarding the relationship between waiting impulsivity/GNG and stopping impulsivity/SST, and our analysis revealed the relationship to be nonsignificant. As expected, impulsive choice/DDT was found to be independent from the other two behavioral dimensions as well (see Table 2 for all correlations between latent variables). With respect to the clinical profiles of behavioral tests, the findings supported all hypotheses: both BPD and ADHD patients showed heightened impulsive choice, and ADHD patients additionally showed heightened stopping and waiting impulsivity (see Table 1).

Table 2. Correlation Table of Latent Variables of the Final Model.

R		1	2	3	4	5	6
1.	Barratt Scale	—	.51***	.40***	.14	.09	−.14*
2.	Deficits in conscientiousness		—	.82***	.13	.19*	−.04
3.	Urgency			—	.25*	.26**	.01
4.	Waiting impulsivity/GNG				—	−.02	−.00
5.	Stopping impulsivity/SST					—	−.04
6.	Impulsive choice/DDT						—

Note. GNG = Go-NoGo task; SST = stop-signal task; DDT = delay discounting task.

Discussion

Based on the literature review and our clinically motivated interest in impulsivity dimensions, we developed a well-fitting CFA model in which existing conceptualizations were modeled as separate dimensions. The model was used to test hypotheses about relationships between personality-related and behavioral dimensions.

Three personality-related dimensions—deficits in conscientiousness, urgency, and the BIS—were found to be related, in that they were correlated in the CFA model and more pronounced among BPD and ADHD patients relative to matched controls. A fourth personality-related dimension—sensation seeking—was excluded from the final model because it was

found to be uncorrelated with all other dimensions and not heightened among patients with BPD or ADHD. It can be concluded that sensation seeking is unrelated to impulsivity in healthy people and patients with BPD and ADHD, which is consistent with previous research (Lopez et al., 2015; MacKillop et al., 2016; Paret et al., 2016).

Meanwhile, the behavioral dimensions were found to be completely unrelated to each other. Lack of correlation between impulsive choice/DDT and impulsive action as measured by GNG and SST has been observed in previous studies (MacKillop et al., 2016; Stahl et al., 2014), but our results further suggest that, while the GNG and SST are both distinguishable from impulsive choice, they should not be considered measures of a single impulsive action dimension. Furthermore, waiting impulsivity/GNG and stopping impulsivity/SST were found to be expressed differently in patients. BPD patients showed no differences from healthy controls in either waiting or stopping impulsivity, but ADHD patients showed increases in both of these dimensions. The results lend support to the existing suggestion that BPD patients are not prone to impulsive action in emotionally neutral situations (Turner et al., 2017). It is, therefore, possible that an emotional variant of GNG (and SST) might better discriminate between some patient groups and controls. Future studies could include emotional variants of GNG and SST in the model (e.g., Hare et al., 2008; Pawliczek et al., 2013). Our results further align with previous findings of impairment in both waiting and stopping impulsivity in patients with ADHD (as in Schachar et al., 2007).

In contrast to previous studies, where the percentage of NoGo commissions was considered the primary index of waiting impulsivity as measured by GNG (as in MacKillop et al., 2016), we found differences between ADHD patients and controls on a dimension measured by three other indices derivable from GNG. In our CFA model, the percentage of NoGo commissions was actually removed from the model due to the low associated regression coefficient. It follows that the deficit of ADHD patients in waiting impulsivity might be driven by attention deficit and response speed abnormalities, but not primarily by the number of action withdrawal failures. Moreover, an increased number of NoGo commissions might constitute a behavioral result of attention and response speed impairment and might be pronounced in challenging situations, since more NoGo commissions are observed in more cognitively demanding tasks (Nieuwenhuis et al., 2003). Thus, inconsistent results regarding a deficit in waiting impulsivity in ADHD patients (Pani et al., 2013; Rubia et al., 2007; Schachar et al., 2007) might follow from taking into account only NoGo commissions, but not considering attention- and response-speed-related task parameters, especially in less cognitively demanding tasks. More confident conclusions to this effect could be drawn if our results were replicated with a more cognitively demanding GNG. Overall, our findings illustrate the importance of evaluating behavioral impulsivity constructs based on multiple indices of global task performance rather than a single variable that might not sufficiently reflect the underlying process leading to impulsivity.

Impulsive choice, as measured by the DDT, was found to be elevated in both patient groups while being uncorrelated with all other dimensions. This result is in agreement with previous studies (Barker et al., 2015; Patros et al., 2016; Turner et al., 2017) and indicates that, regardless of their scores on GNG, SST, and self-report measures, both BPD and ADHD patients tended to prefer immediate rewards over long-term benefits, thus displaying decision making with low sensitivity to consequences. With respect to best practices in the measurement of impulsive choice, our CFA model identified the AUC parameters as more reliable measures than k parameters, since the AUCs were found to load more strongly on the latent variable expressing impulsive choice.

Regarding the associations of self-report-based and behavioral dimensions, several low to very low relationships were observed. Low associations were found between urgency and both dimensions of impulsive action. Comparable correlations have been previously recorded in the literature (Cyders & Coskunpinar, 2011; VanderBroek-Stice, Stojek, Beach, vanDellen, & MacKillop, 2017). Because these associations were observed in the model including healthy participants in our study, it suggests that a link between dimensions of impulsive action and emotional impulsivity exists in the healthy population. In other words, it is possible that the decrease in waiting and stopping associated with a tendency to emotional impulsivity, as known in BPD patients, could, to a lesser degree, apply to healthy people also. Other associations between self-report-based and behavioral measures were found to be very low, although two of them reached borderline significance. Overall, our results correspond with previous studies in that relationships between self-report-based and behavioral dimensions of impulsivity are generally low to very low, although they might reach significance in bigger samples. The most prominent relationship between self-report-based and behavioral impulsivity dimensions based on our study exists between urgency and dimensions of impulsive action.

A limitation of the current study is that the BIS was included among the latent factors in the final CFA model, despite the lack of clarity over its factor structure in preliminary CFAs. Problems with the scale's factor structure have been likewise observed in past studies (e.g., Linhartová et al., 2017; Reise et al., 2013; Vasconcelos et al., 2012). In our study, the scale was retained for its previously demonstrated ability to discriminate between patients and healthy people (Barker et al., 2015; Chamberlain et al., 2017). One direction for improving the fit of the unidimensional structure of the BIS and, consequently, any CFA models incorporating the BIS would be to shorten the scale, leaving only the items with high loadings on a global impulsivity factor. Abbreviated psychometrically sound versions of the BIS

with different factor structures have been already proposed (Morean et al., 2014; Spinella, 2007; Steinberg et al., 2013). A further limitation is that, amid sample size constraints, we were unable to fit the proposed CFA model separately within BPD and ADHD patients to track potential group differences in dimensional interrelationships.

In sum, the latent factor model developed in this study shows that impulsive behaviors can stem from different independent impulsivity subtypes and that underlying impulsivity dimensions can differ in psychiatric patient groups. The results suggest that therapeutical approaches to patients with increased impulsivity can be tailored specifically according to the type of impulsivity in the given patient group. For example, for patients who demonstrate deficits in waiting and stopping impulsivity, training in behavioral inhibition based on the respective behavioral tests would be appropriate (e.g., Melara, Singh, & Hien, 2018; Zhao & Jia, 2019). However, if the dominant dimension is impulsivity under the influence of strong emotions, treatment based on distress tolerance and emotion regulation enhancement can be recommended (such as dialectical behavior therapy, Linehan, 1993). The proposed model can be used for descriptions of impulsivity profiles in psychiatric groups, and thus help to tailor therapy for impulsive patients.

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Notes

1. Robust maximum likelihood fit indices: χ^2 = 1114.655, df = 402, χ^2/df = 2.772, CFI = 0.625, RMSEA = 0.088, SRMR = 0.095
2. Robust maximum likelihood fit indices: χ^2 = 1231.972, df = 405, χ^2/df = 3.041, CFI = 0.565, RMSEA = 0.095, SRMR = 0.095
3. Robust maximum likelihood fit indices: χ^2 = 161.124, df = 85, χ^2/df = 1.895, CFI = 0.963, RMSEA = 0.076, SRMR = 0.088

Supplemental Material

Supplemental material for this article is available online.

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Annex 2

Linhartová, P., Látalová, A., Barteček, R., Širůček, J., Theiner, P., Ejova, A., Hlavatá, P., Kóša, B., Jeřábková, B., Bareš, M., & Kašpárek, T. (2020). Impulsivity in patients with borderline personality disorder: A comprehensive profile compared with healthy people and patients with ADHD. *Psychological Medicine, 50*(11), 1829–1838. doi: 10.1017/S0033291719001892

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Impulsivity in patients with borderline personality disorder: a comprehensive profile compared with healthy people and patients with ADHD

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Original Article

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Abstract

Background. Impulsivity is a core symptom of borderline personality disorder (BPD). Impulsivity is a heterogeneous concept, and a comprehensive evaluation of impulsivity dimensions is lacking in the literature. Moreover, it is unclear whether BPD patients manifest impaired cognitive functioning that might be associated with impulsivity in another patient group, such as ADHD, a frequent comorbidity of BPD.

Methods. We tested 39 patients with BPD without major psychiatric comorbidities and ADHD, 25 patients with ADHD, and 55 healthy controls (HC) using a test battery consisting of a self-report measure of impulsivity (UPPS-P questionnaire), behavioral measures of impulsivity – impulsive action (Go/NoGo task, stop signal task) and impulsive choice (delay discounting task, Iowa gambling task), and standardized measures of attention (d2 test), working memory (digit span), and executive functioning (Tower of London).

Results. Patients with BPD and ADHD, as compared with HC, manifested increased self-reported impulsivity except sensation seeking and increased impulsive choice; patients with ADHD but not BPD showed increased impulsive action and deficits in cognitive functioning. Negative urgency was increased in BPD as compared to both HC and ADHD groups and correlated with BPD severity.

Conclusions. Patients with BPD without ADHD comorbidity had increased self-reported impulsivity and impulsive choice, but intact impulsive action and cognitive functioning. Controlling for ADHD comorbidity in BPD samples is necessary. Negative urgency is the most diagnostically specific impulsivity dimension in BPD.

Introduction

Borderline personality disorder (BPD) is a pervasive mental disorder characterized by disturbed identity, impaired emotion regulation, and marked impulsivity (American Psychiatric Association, 2013). Impulsivity in BPD patients manifests in a range of dangerous and (self-) destructive behaviors such as drug abuse, self-harm, and suicidal behavior and, as such, can lead to serious consequences. However, impulsivity is a heterogeneous concept with several different subtypes associated with different measures that are rarely examined in a complex manner. Comprehensive analysis of impulsivity dimensions can lead to the specification of self-control impairment in a given patient group and, consequently, to tailoring individually suitable forms of psychotherapeutic (Stoffers-Winterling *et al*., 2012) or biological treatment (Lieb *et al*., 2010; Svěrák *et al*., 2018).

Impulsivity is considered either a consequence of some personality traits or a dysfunction of a neurobiological or cognitive function (Linhartová *et al*., 2019). The most up-to-date complex personality model of impulsivity is the UPPS-P questionnaire (Whiteside and Lynam, 2001; Cyders and Smith, 2007). BPD patients have been found to have increased impulsivity in all UPPS-P dimensions except sensation seeking, i.e. in lack of premeditation, lack of perseverance, negative urgency, and positive urgency (Bøen *et al*., 2015; Paret *et al*., 2016). Two broad subtypes of behavioral dimensions of impulsivity were defined in the literature: impulsive action and impulsive choice (Winstanley *et al*., 2006). Impulsive action can be further

divided into waiting impulsivity (difficulties inhibiting premature actions) and stopping impulsivity (difficulties interrupting ongoing actions) (Robinson *et al.*, 2009). In most previous studies, BPD patients have been found to have increased impulsive choice, but intact waiting and stopping impulsivity (Robinson *et al.*, 2009; Jacob *et al.*, 2010; Hagenhoff *et al.*, 2013; Legris *et al.*, 2014; Barker *et al.*, 2015; van Eijk *et al.*, 2015; Berenson *et al.*, 2016; Paret *et al.*, 2017).

Impulsivity manifested in behavioral tests, alongside increased impulsivity itself, may be associated with impaired cognitive functions necessary for task performance such as attention, working memory, and executive functioning (Bazanis *et al.*, 2002; Lampe *et al.*, 2007; Nigg, 2017). Research on cognitive functions in BPD patients has generally produced mixed results (e.g. Feliu-Soler *et al.*, 2013; Hagenhoff *et al.*, 2013). According to a recent meta-analysis, most studies found worse performance in some cognitive domains, but they do not indicate a specific cognitive function in which BPD patients fail consistently (Mcclure *et al.*, 2016).

The diverse results of studies on cognitive functioning in BPD could be related to comorbidities in BPD samples. Some comorbidities, such as major depression, bipolar disorder, and psychotic disorders, are usually excluded from research samples. However, attention-deficit/hyperactivity disorder (ADHD) in BPD patients is often neglected. ADHD is associated with substantial deficits in cognitive functioning. Results of existing meta-analyses suggest that patients with ADHD, in comparison to healthy controls, have worse performance in attention, working memory, planning, and organization (Alderson *et al.*, 2013; Mowinckel *et al.*, 2015; Pievsky and McGrath, 2018). Hence, not controlling for ADHD comorbidity in BPD samples could lead to biased results in tests of cognitive functioning. BPD patients with comorbid ADHD were found to have worse cognitive performance than healthy people and worse than BPD patients without ADHD comorbidity (Lampe *et al.*, 2007). Studies that excluded ADHD comorbidity suggest that BPD patients show deficits in working memory (Stevens *et al.*, 2004; Hagenhoff *et al.*, 2013).

ADHD comorbidity in BPD patients could also lead to distorted impulsivity test results. ADHD patients, as opposed to BPD patients, have been found to have increased waiting and stopping impulsivity (Lampe *et al.*, 2007; Pani *et al.*, 2013). Patients with ADHD and patients with BPD have been found to have increased impulsive choice and UPPS-P dimensions, with the exception of sensation seeking (Toplak *et al.*, 2005; Lopez *et al.*, 2015; Patros *et al.*, 2016; Pedersen *et al.*, 2016), with one study showing higher lack of premeditation and higher lack of perseverance in ADHD patients as compared to BPD patients (Krause-Utz *et al.*, 2016).

Aims and hypotheses

The current study provides a comprehensive evaluation of essential self-reported and behavioral impulsivity dimensions as well as cognitive functions in a sample of patients with BPD who are not affected by ADHD, major depression, bipolar disorder, psychotic disorder, or addiction. The impulsivity profile is compared with a sample of healthy controls and patients with ADHD (without BPD comorbidity). Based on previous research described in the Introduction, we hypothesize that BPD patients, as well as ADHD patients, show increased impulsivity in all UPPS-P subscales except sensation seeking and increased impulsive choice as compared to healthy controls. Further, we hypothesize that BPD patients, unlike ADHD patients, have intact impulsive action as compared to healthy controls. No specific hypotheses were made about cognitive function domains in BPD due to conflicting literature, but we test the hypothesis that only ADHD patients, but not BPD patients, have worse cognitive performance than healthy controls.

Methods

The study was reviewed and approved by the Ethics Committee of University Hospital Brno. Before the research procedure was carried out, the study was explained thoroughly to the subjects who then signed informed consent forms. The research was carried out in accordance with APA ethical standards.

Participants

The study included 39 patients with borderline personality disorder (BPD), 25 patients with attention-deficit/hyperactivity disorder (ADHD), and 55 healthy controls (HC). The HC group was a pooled sample of healthy controls matched to BPD and ADHD patients by age, sex, and education level. HC were recruited through internet advertisement. The Mini international neuropsychiatric interview (MINI; Sheehan *et al.*, 1998) was conducted with the HC to confirm the absence of any mental disorder. The BPD and ADHD patients were recruited at the Department of Psychiatry of the University Hospital Brno and through outpatient psychiatrists in the Czech Republic. The data included available patient documentation, patient charts, mental status examinations, and comprehensive interviews similar in structure to the comprehensive assessment of symptoms and history (Andreasen, Flaum, and Arndt, 1992) focused on patient history, pharmacological history, past symptoms, and the course of the disorder.

The BPD diagnosis was confirmed by two board-certified psychiatrists according to DSM-5 criteria and by a trained psychologist using the Diagnostic Interview for Borderlines – Revised (DIB-R; Zanarini *et al.*, 1989). According to DIB-R, a patient is assessed with BPD if they score at least 8 out of 10 points, with higher scores indicating more severe BPD. In the present sample, 12 patients (31%) scored in DIB-R 8 points, 9 patients (23%) scored 9 points, and 18 patients (46%) scored 10 points. If comorbid ADHD was suspected in the BPD patients, the Diagnostic Interview for ADHD in Adults 2.0 (DIVA 2.0; Kooij and Francken, 2010) was performed to exclude the ADHD comorbidity. For the ADHD sample, the ADHD diagnosis was confirmed by two board-certified psychiatrists according to DIVA 2.0 (Kooij and Francken, 2010). If comorbid BPD was suspected in ADHD patients, the DIB-R (Zanarini *et al.*, 1989) was conducted by a clinical psychologist to assess the comorbidity.

The following comorbidities were excluded from both BPD and ADHD groups according to DSM-5 criteria: major psychiatric disorders with possible influence on impulsive behavior and cognitive functioning, specifically bipolar disorder, major depression, psychotic disorder, addiction; any personality disorder other than BPD in the BPD group; and any personality disorder in ADHD group. The exclusion process was carried out by two board-certified psychiatrists and a clinical psychologist after the interviews and reviewing all aforementioned sources of information about patients.

Characteristics of the samples are presented in Table 1. Details on patient status and medications are presented in online

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Table 1. Descriptive statistics of the samples

	BPD	ADHD	HC	Group comparison
Sex				
Men	$N = 5$	$N = 19$	$N = 20$	BPD *v.* HC: $\chi^2(1) = 6.48$, $p = 0.011$ ADHD *v.* HC: $\chi^2(1) = 10.81$, $p = 0.001$ BPD *v.* ADHD: $\chi^2(1) = 25.95$, $p < 0.001$
Women	$N = 34$	$N = 6$	$N = 35$	
Age	$M = 23.39$	$M = 23.28$	$M = 23.42$	$F(2, 116) = 0.00$, $p = 0.996$
	S.D. = 4.82	S.D. = 8.56	S.D. = 6.34	
Education				
Primary	$N = 11$	$N = 11$	$N = 13$	BPD *v.* HC: Mann-Whitney $U = 1296.00$, $Z = 1.83$, $p = 0.07$ ADHD *v.* HC: Mann-Whitney $U = 808.50$, $Z = 1.69$, $p = 0.09$ BPD *v.* ADHD: Mann-Whitney $U = 435.50$, $Z = -0.49$, $p = 0.63$
Lower secondary	$N = 6$	$N = 1$	$N = 1$	
Higher secondary	$N = 17$	$N = 7$	$N = 26$	
College	$N = 5$	$N = 5$	$N = 15$	
Socio-economic status				
Insufficient	$N = 9$	$N = 0$	$N = 6$	BPD *v.* HC: Mann-Whitney $U = 1430.00$, $Z = 4.01$, $p < 0.001$ ADHD *v.* HC: Mann-Whitney $U = 717.50$, $Z = 0.33$, $p = 0.74$ BPD *v.* ADHD: Mann-Whitney $U = 664.50$, $Z = 3.59$, $p < 0.001$
Unsatisfactory	$N = 17$	$N = 8$	$N = 9$	
Satisfactory	$N = 6$	$N = 10$	$N = 21$	
Very satisfactory	$N = 3$	$N = 7$	$N = 19$	
Depression (MADRS)	$M = 17.69$	$M = 6.64$	$M = 0.82$	$F(2, 116) = 110.842$, $p < 0.001$, $\eta^2 = 0.656$ Bonferroni post-hoc tests: BPD *v.* HC: $t(116) = 14.858$, $p < 0.001$ ADHD *v.* HC: $t(116) = 4.449$, $p < 0.001$ BPD *v.* ADHD: $t(116) = 7.951$, $p < 0.001$
	S.D. = 8.41	S.D. = 4.98	S.D. = 1.57	
Anxiety (SAS)	$M = 49.21$	$M = 40.57$	$M = 28.23$	$F(2, 111) = 86.638$, $p < 0.001$, $\eta^2 = 0.610$ Bonferroni post-hoc tests: BPD *v.* HC: $t(111) = 13.008$, $p < 0.001$ ADHD *v.* HC: $t(111) = 6.511$, $p < 0.001$ BPD *v.* ADHD: $t(111) = 4.312$, $p < 0.001$
	S.D. = 9.44	S.D. = 7.82	S.D. = 5.80	

BPD, borderline personality disorder; ADHD, attention-deficit/hyperactivity disorder; HC, healthy controls; MADRS, Montgomery Åsberg Depression Rating Scale; SAS, Zung self-report anxiety scale.

Supplementary Material. The groups did not differ in age or level of education. BPD and ADHD groups differed in sex, and both groups also differed in sex in comparison with HC as a result of pooling HC matched to BPD patients and HC matched to ADHD patient into one control sample. BPD patients had lower socioeconomic status than both HC and ADHD patients with no difference between the latter two groups. Large differences between the groups were observed in anxiety and depression symptoms, with BPD patients having the highest scores in both variables and ADHD patients having lower scores in both variables than BPD patients, but higher scores than HC.

Procedure

All participants completed clinical and behavioral testing carried out by a trained psychologist within one session lasting approximately two hours.

Clinical and behavioral measures

The subjects underwent a test battery consisting of self-reporting and behavioral tests of impulsivity and cognitive function screening consisting of standardized measures in a fixed order (see online Supplementary Material for details). A validated Czech translation of the UPPS-P scale was used (Linhartová *et al.*, 2017). The UPPS-P has five subscales: lack of premeditation, lack of perseverance, sensation seeking, negative urgency, and positive urgency, with higher scores indicating higher impulsivity. Waiting impulsivity was measured by a Go/NoGo task (GNG), stopping impulsivity by a stop signal task (SST), and impulsive choice by a delay discounting task (DDT) and the Iowa gambling task (IGT). The behavioral tasks were delivered in computerized form, developed in E-Prime 2.0.

Three outcome measures were derived from GNG: *NoGo commissions* (percentage of NoGo trials erroneously followed by a key press), *Go omissions* (percentage of Go trials erroneously followed by no key press), and *Go reaction time* (*Go RT;* average reaction time on correct Go trials). *Stop signal reaction time* (*SSRT*) was derived as the outcome measure from SST by subtracting the average stop signal delay from the average Go RT. The SSRT provides an indication of the average time required for successful stopping; longer SSRTs indicate greater difficulty interrupting actions. Two delayed rewards (DR) were used in DDT: low (approx. 40 EUR) and high (approx. 980 EUR and approx. median salary in the

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Czech Republic at the time of data collection). Two DRs were chosen so that the influence of DR magnitude could be tested, since discounting becomes steeper in low DRs; in other words, people are less willing to wait if the DR is small (Estle *et al.*, 2006; Stanger *et al.*, 2012). *Area under the curve* (AUC; Myerson *et al.*, 2001) was used as the main result from DDT (*AUC low* for the low DR and *AUC high* for the high DR). The lower the AUC, the steeper the discounting, and the higher the impulsive choice. A computerized version of IGT was used (Odum, 2011). The task ended after 200 cards. To track the progress of advantageous decision making, we computed the *net score*, i.e. the difference between the number of cards drawn from advantageous decks (C + D) and the number of cards drawn from disadvantageous decks (A + B), separately for the first and the second half of the task (*1st half net score* and *2nd half net score*).

Working memory was assessed by the Digit Span subtest from the Wechsler Adult Intelligence Scale-III (Wechsler, 1997) with *total score* used as the outcome measure. Executive functioning was measured by the Tower of London (ToL), Drexel University, Second Edition (Culbertson and Zillmer, 2005). Three outcome measures were derived from ToL: *move score* represents the overall efficiency of the participant's problem solving, *initiation time* represents the time spent planning before acting, and *execution time* represents the time needed to solve the task. Attention was assessed by a paper-and-pencil cancellation test d2-R (Brickenkamp *et al.*, 2014). *Speed* (total number of items worked through) and *accuracy* (percentage of errors) scores were derived. Unstandardized scores were used in the analyses to preserve the score variability. Further details on the behavioral and cognitive tests are provided in the online Supplementary Material.

Statistical analysis

Differences in UPPS-P (*lack of premeditation*, *lack of perseverance*, *sensation seeking*, *negative urgency*, and *positive urgency*), GNG (*Go omissions*, *Go reaction time*, and *NoGo commissions*), SST (*stop signal reaction time*), digit span (*total score*), d2 (*speed, accuracy*), and ToL (*move score*, *initiation time*, and *execution time*) were compared between BPD, ADHD, and HC groups in ANOVA with Bonferroni post-hoc tests. DDT was analyzed by repeated-measures ANOVA with Bonferroni post-hoc tests with DR magnitude as a within-subject factor (*AUC low, AUC high*) and group as a between-subject factor. IGT was analyzed by repeated-measures ANOVA with Bonferroni post-hoc tests with time as a within-subject factor (*net score 1st half, net score 2nd half*) and group as a between-subject factor. Moreover, correlations between impulsivity and cognitive and clinical (DIB-R, MADRS, SAS) variables in the three groups were computed. Due to the relatively small sample sizes and the large number of variables, the correlations were not statistically compared between the groups, but significant correlation patterns were examined and commented on.

Results

Table 2 presents descriptive statistics and the results of ANOVAs comparing UPPS-P, GNG, SST, and cognitive tests between the BPD, ADHD, and HC groups. We found that both patient groups as compared to HC have higher lack of premeditation, lack of perseverance, negative urgency, and positive urgency. No group differences were found in sensation seeking. The only significant difference between BPD and ADHD patients was found in negative urgency, with higher scores in BPD patients. In GNG, the ADHD group had significantly more NoGo commissions (i.e. increased waiting impulsivity) than both HC and BPD. The ADHD group also had increased SSRT (i.e. increased stopping impulsivity) as compared to HC and on a trend level as compared to BPD. Regarding the cognitive variables, we found significantly worse performance in working memory in ADHD group as compared to HC and a borderline-significant difference in speed during the attention test, with ADHD having lower speeds than HC. The ADHD group also showed worse performance as compared to HC in executive functions, manifested as higher moves score in ToL.

Descriptive statistics and results of repeated-measures ANOVA of DDT and IGT are displayed in Table 3 and Fig. 1. In DDT, significant effects of DR magnitude, group, and DR*group interaction were observed. Bonferroni post-hoc tests revealed that in the high DR as compared to low DR condition, all groups exhibited a significant increase in AUC ($p < 0.001$ for all the three groups). At the same time, HC showed higher AUC in both low DR and high DR conditions (i.e. lower impulsive choice) than either BPD patients ($p < 0.001$ for both low DR and high DR) or ADHD patients ($p = 0.007$ for low DR, $p < 0.001$ for high DR); there was no difference between the patient groups ($p = 1.000$ for both low and high DR). In IGT, significant effects of time, group, and time*group interaction were observed. Bonferroni post-hoc tests revealed that there were no significant group differences in the net score after the first half of the task ($p = 1.000$ for all intergroup contrasts). Only HC improved significantly from the first to the second half of the task ($p < 0.001$); neither of the patient groups did (BPD: $p = 0.762$; ADHD: $p = 0.570$). HC had higher net scores in the second half of the task than either BPD patients ($p < 0.001$) or ADHD patients ($p = 0.024$) and the two patient groups did not differ ($p = 1.000$).

Relationships between impulsivity and cognitive and clinical variables

Correlation matrices of impulsivity and cognitive and clinical variables are provided in the online Supplementary Materials for the BPD, ADHD, and HC groups separately. The UPPS-P dimensions were generally positively intercorrelated in all the three groups, except sensation seeking (and positive urgency in ADHD), while the behavioral dimensions were generally independent.

In the relationships between impulsivity and cognitive variables, two significant moderate (over $r = 0.4$) correlations were observed in BPD: a negative correlation between NoGo commissions and initiation time (ToL) and a negative correlation between Go omissions and speed (d2 attention test). A number of significant moderate associations were found in ADHD: a positive correlation between digit span and lack of perseverance and IGT, a positive correlation between initiation time (ToL) and Go omissions and IGT, a positive correlation between move score (ToL) and SSRT, and a positive correlation between accuracy (d2 attention test) and Go RT and DDT. In the relationships between impulsivity and clinical variables, the most prominent pattern was that UPPS-P dimensions (except sensation seeking) were positively correlated with DIB-R in BPD. Moreover, negative and positive urgency showed low to moderate positive associations with MADRS and SAS in ADHD and HC.

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Table 2. Descriptive statistics of dependent variables and results of ANOVAs comparing BPD, ADHD, and HC groups

								Bonferroni post-hoc tests		
Variable	Group	*N*	*M*	s.d.	*F* (*df1, df2*)	*p*	η^2	contrasts	*t* (*df*)	*p*
PRE	BPD	39	28.077	5.909	11.246 (2, 116)	<0.001	0.162	BPD *v.* HC	4.405 (116)	<0.001
	ADHD	25	27.320	6.122				ADHD *v.* HC	3.225 (116)	0.005
	HC	55	23.236	4.238				BPD *v.* ADHD	0.563 (116)	1.000
PER	BPD	39	26.487	5.301	17.898 (2, 115)	<0.001	0.237	BPD *v.* HC	5.368 (115)	<0.001
	ADHD	24	26.208	5.949				ADHD *v.* HC	4.375 (115)	<0.001
	HC	55	20.618	4.821				BPD *v.* ADHD	0.206 (115)	1.000
SS	BPD	39	31.051	7.108	1.153 (2, 115)	0.319	0.020	BPD *v.* HC	−0.668 (115)	1.000
	ADHD	24	33.875	7.261				ADHD *v.* HC	1.037 (115)	0.905
	HC	55	32.055	7.181				BPD *v.* ADHD	−1.517 (115)	0.396
NU	BPD	39	38.103	5.276	54.277 (2, 113)	<0.001	0.490	BPD *v.* HC	10.168 (113)	<0.001
	ADHD	22	34.182	6.037				ADHD *v.* HC	5.633 (113)	<0.001
	HC	55	26.309	5.521				BPD *v.* ADHD	2.654 (113)	0.027
PU	BPD	39	38.538	10.265	27.887 (2, 114)	<0.001	0.329	BPD *v.* HC	7.239 (114)	<0.001
	ADHD	23	34.739	8.086				ADHD *v.* HC	4.251 (114)	<0.001
	HC	55	26.018	6.581				BPD *v.* ADHD	1.749 (114)	0.249
Go omissions %	BPD	38	0.106	0.060	1.715 (2, 115)	0.184	0.029	BPD *v.* HC	1.534 (115)	0.383
	ADHD	25	0.109	0.058				ADHD *v.* HC	1.518 (115)	0.395
	HC	55	0.087	0.061				BPD *v.* ADHD	−0.165 (115)	1.000
Go RT	BPD	38	342.783	34.163	1.226 (2, 115)	0.297	0.021	BPD *v.* HC	1.379 (115)	0.512
	ADHD	25	342.649	24.726				ADHD *v.* HC	1.185 (115)	0.715
	HC	55	334.940	21.831				BPD *v.* ADHD	0.019 (115)	1.000
NoGo commissions %	BPD	38	0.281	0.166	6.955 (2, 115)	0.001	0.108	BPD *v.* HC	1.227 (115)	0.667
	ADHD	25	0.380	0.171				ADHD *v.* HC	3.728 (115)	<0.001
	HC	55	0.241	0.139				BPD *v.* ADHD	−2.486 (115)	0.043
SSRT	BPD	39	265.973	92.536	5.063 (2, 116)	0.008	0.080	BPD *v.* HC	0.886 (116)	1.000
	ADHD	25	310.748	53.767				ADHD *v.* HC	3.170 (116)	0.006
	HC	55	251.631	74.352				BPD *v.* ADHD	−2.261 (116)	0.077
Digit span	BPD	39	17.744	4.417	3.323 (2, 116)	0.040	0.054	BPD *v.* HC	−1.076 (116)	0.853
	ADHD	25	16.080	4.142				ADHD *v.* HC	−2.573 (116)	0.034
	HC	55	18.691	4.082				BPD *v.* ADHD	1.543 (116)	0.376
d2 (speed)	BPD	38	176.500	38.198	3.040 (2, 115)	0.052	0.050	BPD *v.* HC	−1.375 (115)	0.516
	ADHD	25	166.160	36.640				ADHD *v.* HC	−2.403 (115)	0.054
	HC	55	186.855	33.443				BPD *v.* ADHD	1.125 (115)	0.789
d2 (accuracy)	BPD	38	8.424	8.830	0.128 (2, 115)	0.880	0.002	BPD *v.* HC	0.485 (115)	1.000
	ADHD	25	8.213	6.937				ADHD *v.* HC	0.306 (115)	1.000
	HC	55	7.666	6.505				BPD *v.* ADHD	0.111 (115)	1.000
ToL moves	BPD	38	22.263	14.099	3.590 (2, 113)	0.031	0.060	BPD *v.* HC	0.942 (113)	1.000
	ADHD	24	29.625	21.986				ADHD *v.* HC	2.680 (113)	0.025
	HC	54	19.056	14.234				BPD *v.* ADHD	−1.756 (113)	0.245
ToL init. time	BPD	38	85.719	55.469	1.161 (2, 111)	0.317	0.020	BPD *v.* HC	−1.514 (111)	0.399
	ADHD	23	98.107	89.785				ADHD *v.* HC	−0.701 (111)	1.000
	HC	53	112.882	98.021				BPD *v.* ADHD	−0.556 (111)	1.000

(*Continued*)

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Table 2. (*Continued.*)

								Bonferroni post-hoc tests		
Variable	Group	*N*	*M*	S.D.	*F* (*df1, df2*)	*p*	η^2	contrasts	*t* (*df*)	*p*
ToL exec. time	BPD	38	194.498	96.181	0.222 (2, 111)	0.802	0.004	BPD *v.* HC	−0.365 (111)	1.000
	ADHD	23	211.306	85.658				ADHD *v.* HC	0.391 (111)	1.000
	HC	53	201.942	99.835				BPD *v.* ADHD	−0.663 (111)	1.000

BPD, borderline personality disorder; ADHD, attention-deficit/hyperactivity disorder; HC, healthy controls; PRE, lack of premeditation; PER, lack of perseverance; SS, sensation seeking; NU, negative urgency; PU, positive urgency; Go RT, Go reaction time; SSRT, stop signal reaction time; ToL, Tower of London; init. Time, initiation time; exec. time, execution time; MADRS, Montgomery Åsberg Depression Rating Scale; SAS, Zung self-reported anxiety scale.

Table 3. Descriptive statistics and results of ANOVA for delay discounting and Iowa gambling task

Variable	Group	*N*	*M*	S.D.	*F* (*df1, df2*)	*p*	$_p\eta^2$
DDT AUC low	BPD	39	0.310	0.242	*Group effect*		
	ADHD	25	0.328	0.269	17.77 (2, 114)	<0.001	0.24
	HC	53	0.545	0.243	*Delayed reward magnitude effect*		
DDT AUC high	BPD	39	0.551	0.289	197.45 (1, 114)	<0.001	0.63
	ADHD	25	0.503	0.299	*Interaction effect*		
	HC	53	0.824	0.190	3.17 (2, 114)	0.046	0.05
IGT 1st half net score	BPD	39	6.41	29.59	*Group effect*		
	ADHD	25	10.96	40.77	7.09 (2, 115)	0.001	0.11
	HC	54	21.63	37.39	*Time effect*		
IGT 2nd half net score	BPD	39	18.15	44.73	35.67 (1, 115)	<0.001	0.24
	ADHD	25	26.56	56.99	*Interaction effect*		
	HC	54	58.67	42.03	6.08 (2, 115)	0.003	0.10

BPD, borderline personality disorder; ADHD, attention-deficit/hyperactivity disorder; DDT, delay discounting task; HC, healthy controls; IGT, Iowa gambling task; AUC, area under the curve. *Note*. In DDT: delayed reward magnitude is a within-subject factor, group is a between-subject factor. In IGT: time is a within-subject factor (1st half *v.* 2nd half of the task), group is a between-subject factor.

Discussion

Self-reported impulsivity

Our results confirm previous research in that both the BPD patients and the ADHD patients, in comparison with HC, manifested increased lack of premeditation, lack of perseverance, and positive and negative urgency. Neither patient group manifested elevated sensation seeking. We found that BPD patients had higher negative urgency than the HC and ADHD groups, with the highest effect size of the intergroup contrast from all impulsivity variables.

The concept of negative urgency combines affective instability and impulsivity, and the importance of this combination for BPD was stressed in previous studies (Tragesser and Robinson, 2009; Sebastian *et al.*, 2013; Barteček *et al.*, 2019). Negative urgency was found to be associated with BPD features in non-clinical samples (Tragesser and Robinson, 2009; DeShong and Kurtz, 2013; Peters *et al.*, 2013, 2017), and increased in BPD patients as compared to patients with antisocial personality disorder (Taherifard *et al.*, 2015) and to patients with bipolar disorder (Bøen *et al.*, 2015). Thus, markedly increased negative urgency seems to be specific for BPD patients even in comparison with other impulsive patient groups and constitutes a possible marker for BPD. Comparisons of negative urgency between BPD patients and patients with other impulsive disorders, such as patients with addiction or eating disorders, would be beneficial in future studies.

Negative urgency was found to be associated with self-harm or partner violence (Peters *et al.*, 2013, 2017) in non-clinical samples and with suicidal attempts and healthcare utilization in BPD patients (Barteček *et al.*, 2019). BPD patients show elevated not only negative, but also positive urgency (Bøen *et al.*, 2015; Paret *et al.*, 2016). Positive urgency was found to be associated with several types of risky behavior in other than BPD samples, such as with substance abuse, compulsive buying, or risky sexual behavior in non-clinical samples (Zapolski *et al.*, 2009; Rose and Segrist, 2014; Dinc and Cooper, 2015) and with risky behavior in patients with PTSD (Weiss *et al.*, 2015). In general, positive urgency received less attention than negative urgency in the literature on BPD. This might relate to the fact that negative affect states, but not positive, are related to self-harming and suicidal behavior in BPD. However, BPD patients also experience negative emotions more often than healthy people (Nica and Links, 2009; Steenkamp *et al.*, 2015; Law *et al.*, 2016). In other words, patients with BPD not only tend to act impulsively in intense emotional states, but they also have a higher chance of experiencing intense negative emotional states, in which they are prone to self-harming and life-threatening behavior. This typical pattern seems to be captured by highly elevated negative urgency in BPD patients.

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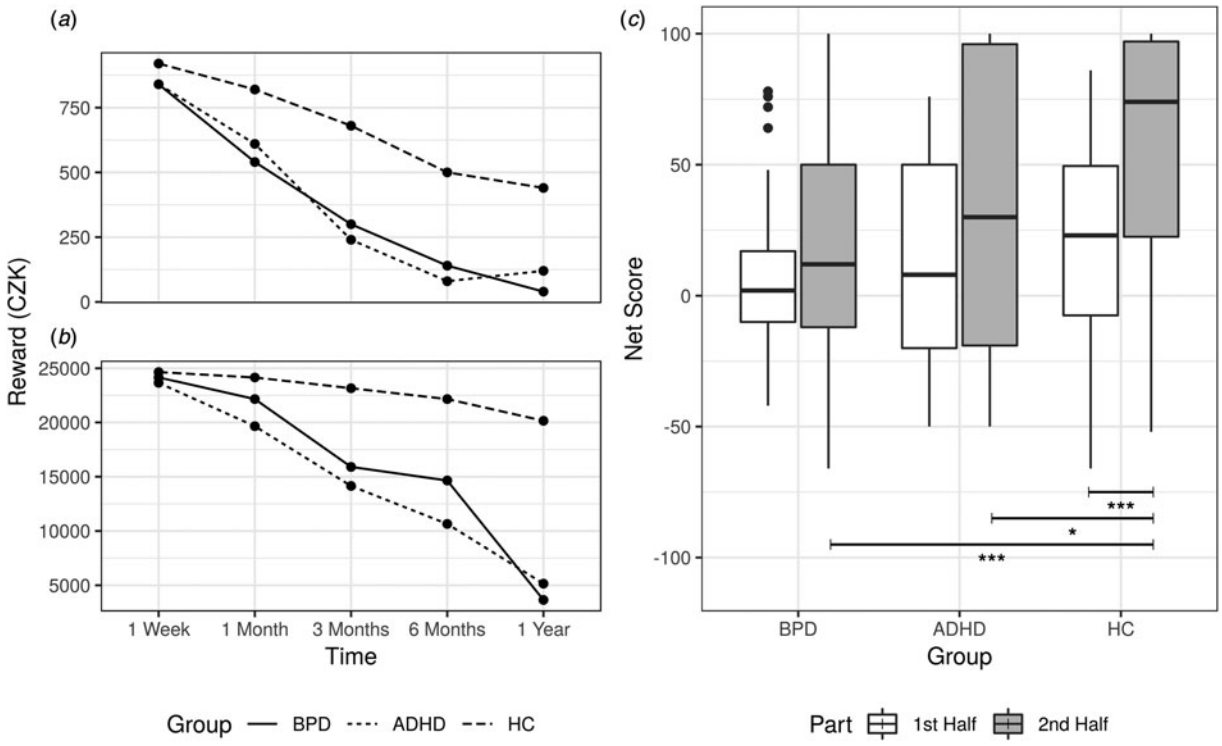

Fig. 1. (a) Results of delay discounting for low delayed reward, (b) Results of delay discounting for high delayed reward, (c) Results of Iowa gambling task. *Note.* (a) Median indifference points from delay discounting with low delayed reward in Czech *koruna* (CZK; y axis) with delay on x axis per group. (b) Median indifference points from delay discounting with high delayed reward in Czech *koruna* (y axis) with delay on x axis per group. (c) Boxplots of net scores per groups split for the first and the second half of the task. Net score was computed by counting frequency of cards drawn from the four decks according to the following equation: (C + D) − (A + B). Higher scores indicate more advantageous decision making.*$p < 0.05$, ***$p < 0.001$.

In contrast to the study by Krause-Utz *et al.* (2016), we found no differences in lack of perseverance or lack of premeditation between the patient groups. A possible confounding variable might be sex, which was not equally distributed in the patient groups in our study. Future studies could explore the role of sex in UPPS-P dimensions in BPD and ADHD patients.

Behavioral impulsivity

Our results showed that impulsive action, i.e. both the ability to withhold premature actions (waiting impulsivity) and to stop ongoing actions (stopping impulsivity), is intact in BPD patients; these results are similar to previous studies (under emotionally neutral circumstances; Jacob *et al.*, 2010; Cackowski *et al.*, 2014; Barker *et al.*, 2015; Krause-Utz *et al.*, 2016). Impulsive action was elevated in ADHD patients as compared to HC, similarly as in previous studies (Lampe *et al.*, 2007; Pani *et al.*, 2013). We also found close-to-significant differences in both waiting (NoGo commissions) and stopping (SSRT) impulsivity between patients with BPD and ADHD. Thus, the elevation in impulsive action seems to be specific for the ADHD group; and it is not present in patients with BPD.

On the other hand, BPD patients and ADHD patients showed increased impulsive choice in both relevant tasks. As expected, all the three groups showed less steep delay discounting in the high DR condition as compared to low DR condition. In other words, all the participants were willing to wait longer for the delayed reward that had a high value. Both patient groups had steeper delay discounting in both low and high DR conditions than HC did, as in previous studies (Patros *et al.*, 2016; Paret *et al.*, 2017). In sum, BPD patients, as well as ADHD patients, exhibit a higher preference for immediate rewards than HC regardless of delayed reward magnitude.

In the Iowa gambling task, both patient groups showed less advantageous decision-making than HC, as in previous studies (Toplak *et al.*, 2005; Paret *et al.*, 2017), but only after the second half of the task, i.e. after 200 cards. This result was due to the fact that HC improved during the task; the patient groups did not. We administered the prolonged IGT version containing 200 cards since it was previously shown that the standard 100 cards might not be sufficient to learn advantageous decision-making, even in healthy people (Fernie and Tunney, 2006). Our data support this hypothesis by showing that a longer time (i.e. 200 cards) was needed to detect group differences between HC and impulsive patients. To sum, both BPD patients and ADHD patients manifested impairment in IGT, indicating a reduced ability to learn from consequences and increased impulsive decision making, but this difference was not shown earlier than after the second half of the prolonged task.

Cognitive functions

The results of cognitive tests in our study are clear: as compared to HC, BPD patients did not show any deficit in cognitive functioning; ADHD patients manifested deficits in attention, working memory, and executive functioning. However, there were no significant differences in the cognitive tests between the two patient groups. This pattern of results is due to the fact that in all the

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variables with significant differences between the ADHD group and HC, the BPD patients scored on average between the ADHD patients and HC. Our results support studies that excluded ADHD comorbidity and found no attention deficit in BPD patients as compared to HC (Lampe *et al.*, 2007; Hagenhoff *et al.*, 2013) and lend further support to the hypothesis that the attention deficits in BPD patients observed in some studies might have been driven by ADHD comorbidity. Evidence about deficits of BPD patients in executive functioning remains limited, and our study supports the hypothesis that executive functioning of patients with BPD is usually intact.

However, impaired working memory in BPD patients was previously found in studies that excluded ADHD comorbidity (Stevens *et al.*, 2004; Hagenhoff *et al.*, 2013). Differences in the literature could be also influenced by the heterogeneity of working memory measures used in the studies. For example, in our study we used a relatively straightforward and short working memory test; both previously mentioned studies used more complex and possibly more demanding tests, like computerized n-back tasks (Stevens *et al.*, 2004; Hagenhoff *et al.*, 2013). It is possible that BPD patients without ADHD comorbidity could show some cognitive impairment only in highly demanding situations. It is also possible that highly demanding tasks could induce stress levels that influence the cognitive performance of BPD patients, similarly as high stress levels were found to increase impulsive action in BPD (Krause-Utz *et al.*, 2016). Future studies should explore the question of whether BPD patients fail in highly demanding working memory tasks as compared to less demanding tasks and, if such impairment was found, whether it could have been caused by higher stress levels during demanding tasks as opposed to insufficient cognitive function capacity.

More support for the importance of emotions in cognitive functioning in BPD can be drawn from the perspective of comparison between performances in ToL and IGT. ToL can be considered a measure of 'cool', i.e. emotionally neutral, executive functioning requiring predominantly cognitive planning and correct execution of the plan (Chan *et al.*, 2008). On the other hand, IGT can be considered a measure of 'hot' executive functions that include an emotional aspect by providing a rewards and punishments (gains and losses) environment (Chan *et al.*, 2008). Importantly, BPD patients showed impairment only in IGT, but their decision-making was intact in ToL.

Relationships between impulsivity and cognitive and clinical variables

Our study confirms the results of the previous studies (MacKillop *et al.*, 2016; Linhartová *et al.*, 2019) in that dimensions of self-reported impulsivity are related, while low to very low correlations are present between behavioral tests of impulsivity. Worse performance in attention and working memory was associated with higher impulsive choice, and worse performance in executive functioning was associated with higher stopping impulsivity and higher impulsive choice in patients with ADHD. Similar associations were not present in patients with BPD or in HC. The results indicate that impulsivity in ADHD is more closely linked with cognitive functions than in BPD.

Importantly, we found moderate positive correlations of BPD severity with all the UPPS-P subscales except sensation seeking. BPD severity was not correlated with any other variable including depression and anxiety symptoms. This result puts more emphasis on the importance of impulsivity for BPD patients.

Limitations

The differences in sex and inpatient/outpatient status between the BPD and ADHD samples can be considered as a limitation of our study. However, our sample has high ecological validity, since there is a prevalence of women among BPD patients and a prevalence of men among ADHD patients in clinical samples (American Psychiatric Association, 2013). Both sex and inpatient/outpatient status influence could not have been tested, since the vast majority of the BPD patients were women and inpatients, and the majority of the ADHD patients were men and all the ADHD patients were outpatients. However, we acknowledged the state severity of the patients by measuring depression and anxiety symptom levels. It can be viewed as a possible limitation that a single pooled sample of healthy controls was used for comparison with the patient groups. However, this approach was chosen to strengthen the statistical power of the analyses and to enable direct comparison of the two patient groups within ANOVA. Further, the influence of several possible confounding variables on impulsivity, specifically depression and anxiety symptoms, could not have been tested directly in the linear models due to small sample sizes for such a complex analysis. However, we included depression and anxiety in the correlation analysis to track a possible interrelatedness with impulsivity or cognitive measures. The differences between the groups in correlations were not statistically tested due to the high number of variables included in this analysis. Thus, the results should be interpreted carefully and should serve as hypotheses-generating rather than definite results.

Conclusion

Comprehensive analysis of impulsivity measures showed that the major diagnostically specific contributor to impulsive behavior in patients with BPD is negative urgency. BPD patients, unlike ADHD patients, do not show impairments in impulsive action and their cognitive functions seem to be intact. Thus, it is crucial to distinguish the ADHD comorbidity in BPD samples.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291719001892.

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Conflict of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Annex 3

Barteček, R., Hořínková, J., **Linhartová, P.,** & Kašpárek, T. (2019). Emotional impulsivity is connected to suicidal attempts and health care utilization in patients with borderline personality disorder. *General Hospital Psychiatry,* 56, 54–55.
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Letter to the Editor

Emotional impulsivity is connected to suicide attempts and health care utilization in patients with borderline personality disorder

ARTICLE INFO

Keywords:
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Dear Editor,

Borderline personality disorder (BPD) is a psychiatric disorder with extensive healthcare utilization [1]. One of the symptom clusters of BPD relates to impulsivity – a complex construct that can be described as acting on the spur of the moment without considering the consequences. It can lead to a broad spectrum of clinically relevant behaviors including self-harm and aggressive acts [2] that may be connected to healthcare utilization, such as hospitalization and medication usage.

UPPS-P is an impulsivity model based on several personality traits that include measures of impulsive behavior during the experience of intense emotions. It consists of five factors: (lack of) perseverance, (lack of) premeditation, sensation seeking, positive and negative urgency (tendency to act impulsively under the influence of positive or negative emotions) [3]. With its emphasis on impulsivity caused by intense emotions, this model seems to be a suitable measure of impulsivity in BPD.

Previous works found that impulsivity, especially negative urgency, played a role in the suicidal, self-harming [4], and aggressive behaviors [5]; however, information about its role in healthcare utilization is scarce.

To help fill gaps in the knowledge about the relationship between impulsivity facets, clinically relevant behavior, and healthcare utilization, we conducted a cross-sectional study in BPD patients who sought clinical care at the department of psychiatry of a general hospital offering care for a metropolitan area with approximately 800,000 inhabitants. Eligible patients were between the ages of 18 and 35 and without major psychiatric or neurologic comorbidities. Diagnosis of BPD was confirmed by two board-certified psychiatrists according to DSM V [1].

We documented two variables reflecting clinically relevant behavior: lifelong count of suicide attempts (Suicidality), and number of physically aggressive acts in the last two years (Aggression); and two variables reflecting healthcare utilization: lifetime count of hospitalizations (Hospitalizations), and lifetime count of psychiatric medications (Medication).

Every treatment with a psychiatric drug lasting at least two weeks was recorded. Anxiolytics other than buspirone, gabapentin, and pregabalin were not included. Next, patients were examined using the UPPS-P scale [3] to describe impulsivity facets. Because evaluated variables were counts and did not follow normal distribution, Poisson regression was used to define relationships between impulsivity facets, age, and clinically important variables, with significance set to $p < 0.01$ (Bonferroni corrected).

45 BPD patients were enrolled (37 females; median of age 22 years). The use of medication in our sample was extensive: 88.24% had been administered at least one psychotropic drug for longer than two weeks; 82.35% had undergone treatment with antidepressants; 64.71% with antipsychotics; 23.53% with anxiolytics; and 20.59% with mood stabilizers. The four most common drugs were quetiapine, sertraline, escitalopram, and mirtazapine. Analysis of relationships between clinical or health-care utilization parameters and UPPS-P factors showed significant connection between Hospitalizations and Suicidality, Suicidality and Negative urgency, Suicidality and Sensation seeking, Aggression and Negative urgency, and Medication and Negative urgency. The properties of Poisson regression models and results are summarized in the Table 1.

Our study showed an importance of negative urgency in suicidal and aggressive events in BPD – a finding supported by previous works [4–6]. Negative urgency can be considered a mediator between negative emotions and impulsive behavior [3]. Because another symptom cluster in BPD, emotional dysregulation, increases the risk of negative affect [1], it is probable that the interaction between emotional dysregulation and impulsivity is critical for the emergence of clinically relevant behavior.

Another important finding was the relationship between the number of suicide attempts and the number of hospitalizations. It suggests that a significant number of hospitalizations in BPD patients may be a consequence of suicide attempts [7].

Interestingly, our results concerning medication use contradict previous studies that found that affective symptoms, not impulsivity, were an indication for pharmacotherapy in most BPD patients [8,9]. This may be a consequence of different impulsivity measures employed in previous studies – earlier impulsivity models tended to omit emotional impulsivity, i.e. urgency. It is possible that concepts implementing a connection between emotions and impulsivity, such as

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Table 1
Regression models of relationships between impulsivity facets and clinical impacts.

Model	Distribution	Dependent variable	Independent variable	Coefficient (95% CI)	Z	P	
1	Quasi	HOS	SUI	0.281 (0.116, 0.445)	3.364	0.002	***
			AGG	0.016 (−0.154, 0.170)	0.200	0.84	
2	Quasi	MED	SUI	0.037 (−0.133, 0.197)	0.441	0.66	
			AGG	0.032 (−0.127, 0.167)	0.426	0.67	
3	Poiss	SUI	Age	0.041 (0.001, 0.081)	2.007	0.04	*
			NU	0.121 (0.061, 0.183)	3.912	< 0.001	***
			PR	−0.001 (−0.056, 0.056)	−0.051	0.96	
			PE	−0.038 (−0.102, 0.026)	−1.180	0.24	
			PU	−0.005 (−0.045, 0.035)	−0.239	0.81	
			SS	0.054 (0.018, 0.092)	2.876	0.004	***
4	Quasi	AGG	Age	0.070 (0.007, 0.133)	2.198	0.03	*
			NU	0.177 (0.074, 3.179)	3.179	0.003	***
			PR	−0.060 (−0.135, 0.035)	−1.254	0.22	
			PE	0.063 (−0.041, 0.175)	1.140	0.26	
			PU	−0.012 (−0.080, 0.053)	−0.356	0.72	
			SS	0.010 (−0.051, 0.072)	0.326	0.75	
5	Poiss	MED	Age	0.011 (−0.031, 0.054)	0.523	0.60	
			NU	0.096 (0.048, 0.146)	3.875	< 0.001	***
			PR	−0.005 (−0.055, 0.046)	−0.186	0.85	
			PE	−0.029 (−0.086, 0.030)	−0.976	0.33	
			PU	0.008 (−0.023, 0.039)	0.498	0.62	
			SS	−0.019 (−0.050, 0.011)	−1.243	0.21	
6	Quasi	HOS	Age	0.048 (−0.002, 0.097)	1.891	0.07	
			NU	0.097 (0.024, 0.174)	2.556	0.01	*
			PR	−0.020 (−0.090, 0.054)	−0.555	0.58	
			PE	−0.012 (−0.091, 0.069)	−0.304	0.76	
			PU	0.003 (−0.048, 0.054)	0.116	0.91	
			SS	0.010 (−0.031, 0.052)	0.462	0.65	

Test for Overdispersion by Cameron & Trivedi at $p = 0.05$ [10] was used. In case of positivity of the test, quasipoisson distribution was assumed.
Abbreviations: quasi – quasipoisson distribution, poiss – Poisson distribution, HOS – hospitalizations, MED – medication, SUI – suicidality, AGG – aggressivity, NU – negative urgency, PR – (lack of) premeditation, PE – (lack of) perseverance, PU – positive urgency, SS – sensation seeking. Regression results: Statistically significant relationships are highlighted: *** – result did survive Bonferroni correction ($p < 0.01$), * – result did not survive Bonferroni correction ($p < 0.05$).

UPPS-P, are more sensitive to detect the link between impulsivity and extensive medication use in BPD.

To conclude, negative urgency was important in clinically relevant behavior and healthcare usage. This impulsivity facet could therefore be used as a risk-assessment tool. Because negative urgency implements the combination of negative affect regulation and impulsivity, both of these processes should be addressed in a clinical setting to limit suicidal or aggressive behavior and healthcare utilization in BPD.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genhosppsych.2018.11.008.

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Annex 4

Hlavatá, P., **Linhartová, P.,** Šumec, R., Filip, P., Světlák, M., Baláž, M., Kašpárek, T., & Bareš, M. (2020). Behavioral and Neuroanatomical Account of Impulsivity in Parkinson's Disease. *Frontiers in Neurology*, 10, 1338. doi: 10.3389/fneur.2019.01338

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Behavioral and Neuroanatomical Account of Impulsivity in Parkinson's Disease

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Impulse control disorder (ICD) is a major non-motor complication of Parkinson's disease (PD) with often devastating consequences for patients' quality of life. In this study, we aimed to characterize the phenotype of impulsivity in PD and its neuroanatomical correlates.

Methods: Thirty-seven PD patients (15 patients with ICD, 22 patients without ICD) and 36 healthy controls underwent a neuropsychological battery. The test battery consisted of anxiety and depression scales, self-report measures of impulsivity (Barratt scale and UPPS-P), behavioral measures of impulsive action (Go/No-Go task, Stop signal task) and impulsive choice (Delay discounting, Iowa gambling task), and measures of cognitive abilities (working memory, attention, executive function). Patients and controls underwent structural MRI scanning.

Results: Patients with ICD had significantly higher levels of self-reported impulsivity (Barratt scale and Lack of perseverance from UPPS-P) in comparison with healthy controls and non-impulsive PD patients, but they performed similarly in behavioral tasks, except for the Iowa gambling task. In this task, patients with ICD made significantly less risky decisions than patients without ICD and healthy controls. Patients without ICD did not differ from healthy controls in self-reported impulsivity or behavioral measurements. Both patient groups were more anxious and depressive than healthy controls. MRI scanning revealed structural differences in cortical areas related to impulse control in both patient groups. Patients without ICD had lower volumes and cortical thickness of bilateral inferior frontal gyrus. Patients with ICD had higher volumes of right caudal anterior cingulate and rostral middle frontal cortex.

Conclusions: Despite the presence of ICD as confirmed by both clinical follow-up and self-reported impulsivity scales and supported by structural differences in various neural nodes related to inhibitory control and reward processing, patients with ICD performed no worse than healthy controls in various behavioral tasks previously hypothesized as robust impulsivity measures. These results call for caution against impetuous interpretation of

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behavioral tests, since various factors may and will influence the ultimate outcomes, be it the lack of sensitivity in specific, limited ICD subtypes, excessive caution of ICD patients during testing due to previous negative experience rendering simplistic tasks insufficient, or other, as of now unknown aspects, calling for further research.

Keywords: impulse control disorder, Parkinson's disease, impulsive action, impulsive choice, structural MRI, Iowa gambling task, delay discounting task, stop signal task

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease characterized not only by motor symptoms as rigidity, hypokinesis, and tremor, but also by a variety of non-motor deficits. Among these non-motor symptoms, impulse control disorder (ICD) is the one that has a devastating effect on the quality of patients' life. In the population of PD patients, ICD manifests itself in a wide spectrum of impulsive behaviors such as pathological gambling, binge eating, hypersexuality, excessive shopping, and also repetitive excessive behaviors like punding (stereotyped purposeless repetitive behavior), hobbyism (internet use, reading, art work), walk-abouts (purposeless wandering), and hoarding (1, 2).

ICD in PD is usually believed to be a consequence of dopaminergic treatment (2, 3), but recent studies claim that there is an interaction of medication influence with underlying vulnerability to impulsive behavior (4, 5). Therefore, it is important to describe the behavioral pattern and neurobiological correlates of impulsivity in PD to track possible correlates of ICD in PD patients. Impulsivity is a heterogeneous concept, which can be understood as a personality trait or as a consequence of a neurobiological function deficit. Behavioral models of impulsivity distinguish impulsive action, which means inability to inhibit prepotent or unwanted actions (waiting impulsivity) or inability to stop ongoing action (stopping impulsivity), and impulsive choice, which includes aspects like high sensitivity to reward, risk taking, and preference of small immediate rewards to long-term gains (6). Impulsivity as a personality trait is measured by self-reported questionnaires, such as the Barratt scale or the UPPS-P scale; impulsivity as neurobiological deficit is measured by behavioral tasks.

Research using self-reported methods concluded that people with certain personality traits are in higher risk of developing ICD. Specifically, associations between ICD and higher novelty/sensation seeking, compulsivity, depression, and anxiety were found (3, 7–9). Impulsive personal traits have been previously associated with ICD in PD. Patients with ICD manifest elevated self-impulsivity in the Barratt scale (9, 10). Other risk factors for developing ICD in PD patients are younger age/younger age of disease onset, family history of behavior such as gambling or alcoholism, being man, and being single (2, 8, 11–14).

Previous research revealed increased impulsive choice, i.e., increased tendency to risky or disadvantageous decisions in general PD population (i.e., ICD status was not reported) (15–23) or in PD-ICD patients specifically (9, 24, 25). A tendency to irrational choices and early decisions in the Bead task, a test of reflection impulsivity, was observed in PD-ICD patients (26). These patients collected less information than PD patients without ICD or healthy controls before making a decision. However, results are not consistent. Study of Voon et al. (27) reported that PD-ICD patients have greater tendency to risk in comparison with patients without ICD, but only when there is only gain possibility, not in a situation with possibility of loss. Several studies did not find any differences in choice impulsivity between PD-ICD patients and healthy controls or PD patients without ICD (28–30) or in general PD population (31, 32). One study reported only statistical trend toward more risky decisions in the PD-ICD group in the Iowa gambling task (10). No significant differences in the performance between patients with and without ICD were reported in the Balloon Analog Risk Task (33–35). Ambivalent results were obtained regarding learning from the negative feedback. Several studies found lower sensitivity to negative feedback in PD-ICD (33, 36, 37), but others found no differences between ICD and patients without ICD or healthy controls (11, 35). Moreover, PD-ICD patients without medication showed decreased learning from negative feedback and increased learning from positive feedback compared to the PD-ICD patients on medication (11). Patients with ICD on dopamine agonists make faster decisions and more impulsive choices than patients off medication (28) and show enhanced sensitivity to risk (27).

Several studies reported increased stopping impulsivity (38–41) and waiting impulsivity (42) in the general PD population. However, there are also reports of intact impulsive action in PD patients without ICD (43) and in PD patients in general (ICD not specified) (44). Studies conducted on PD-ICD patients brought evidence of intact impulsive action (10, 45, 46); one study reported even faster Stop signal reaction time (SSRT), which means better ability to stop ongoing actions, i.e., lower stopping impulsivity in PD-ICD patients (43).

Structural imaging methods found evidence of cortical thickness abnormalities in PD-ICD in the structures related to impulse control and decision making, namely, the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), and corpus callosum (47–51). A gray-matter volume loss in amygdala and orbitofrontal cortex and volume changes in nucleus accumbens (NAcc) and in amygdala were observed in PD-ICD (21, 47, 48, 52).

There are only few studies directly comparing PD patients with and without ICD in impulsivity domains. Moreover, individual studies usually do not target multiple impulsive domains simultaneously, despite the heterogeneous nature of

impulsivity. The aim of our study was to describe the phenotype of impulsivity in PD patients with and without ICD by testing multiple impulsivity domains. We included three groups into our research: PD patients with ICD (PD-ICD), PD patients without ICD (PD-nonICD) and healthy controls (HC). We used self-reported impulsivity questionnaires (the UPPS-P and the Barratt scale), behavioral tasks for assessment of impulsive action (Go/No-Go task, Stop signal task), and impulsive choice (Iowa gambling task, Delay discounting task). We also measured depression, anxiety, and cognitive components influencing performance in impulsivity tasks (attention, working memory, and executive functioning). Moreover, structural magnetic resonance images (MRI) were obtained. We analyzed several brain regions, which were previously in the literature linked to impulsivity, inhibitory control, and decision making (**Table 3**).

Based on previous research, we hypothesized that PD patients with ICD, but not those without ICD, show greater impulsivity in self-reported scales. Further, we hypothesized that only PD-ICD patients show increased impulsivity in the Sensation seeking subscale of UPPS-P in comparison with healthy controls. We did not make any specific hypotheses for the other UPPS-P dimensions due to the lack of literature. We expect greater impulsive choice in the PD-ICD population, but intact impulsive action. No specific hypotheses were made about impulsive action and impulsive choice in patients without ICD due to conflicting literature and lack of literature targeting specifically PD patients without ICD. We expected PD-ICD patients to show brain structure abnormalities in comparison with healthy controls in the prefrontal cortex (orbitofrontal cortex, ACC, and DLPFC) and NAcc.

METHODS

Subjects

Thirty-seven patients with Parkinson's disease and 36 healthy controls took part in this study; the groups were matched by age, gender, education, and laterality. All patients were recruited from the University Hospital of St. Anne, Brno, Czech Republic. Healthy volunteers were recruited by advertising in local newspapers. Patients aged 25–75 with a diagnosis of Parkinson's disease based on the UK Brain Bank Criteria (53) were recruited in the study. All patients were under dopaminergic medication for at least 12 months preceding the examination and had stable doses at least for 4 weeks before testing. Exclusion criteria for all subjects were neurological or systemic disorder with effect on brain function (except PD in the patient groups), lesions in MRI scans, comorbid psychotic disease, affective disease or autism spectrum disorder, mental retardation, cognitive deficit (MMSE under 27), severe depression, and substance abuse.

Prior to the testing, data about age of the PD onset, Hoehn and Yahr stage, and medication calculated as levodopa equivalent dose were obtained, and cognition was examined using MMSE. Healthy volunteers were assessed by the Mini international neuropsychiatric interview [MINI; (54)] to exclude any subjects with psychiatric symptoms. The patients had no self-reported cognitive problems; none of them scored below 28 in Mini-Mental State Examination [MMSE; (55)]. Most of the patients were in stage 2 or 3 according to the Hoehn and Yahr Scale (56). Fifteen patients had ICD, and 22 patients were without ICD. Patients with ICD were selected by a neurologist based on interview with the patient and presence of ICD signs in their medical records. Only patients with severe behavioral problems connected to ICD were recruited. The patients showed the following ICD symptoms: gambling (5 patients), binge eating (3 patients), hypersexuality (2 patients), hobbyism (1 patient), compulsive buying (1 patient), hoarding (1 patient), punding (1 patient), pedantry (1 patient), and excessive cleaning (1 patient). Some of the patients showed more than one symptom of ICD. The study was approved by the Institutional Ethical Committee. All participants signed the informed consent prior to the beginning of the procedure. Characteristics of the sample are summarized in **Table 1**.

Experimental Procedure

Subjects underwent a neuropsychological battery of tests and questionnaires and performed four computerized behavioral tasks. The test battery included the Barratt scale (57) and the UPPS-P scale (58–60) for measuring self-reported impulsivity, the Montgomery-Asberg Depression Rating Scale (61), the Zung Self-Rating Anxiety Scale (62), and standardized measures of cognitive functions. Waiting impulsivity was measured by the Go/No-Go task (GNG), stopping impulsivity was measured by the Stop signal task (SST), and impulsive choice was assessed by the Delay discounting task (DDT) and the Iowa gambling task (IGT). Results are summarized in **Table 2**. Behavioral tests were created in E-Prime 2.0 software. The whole testing procedure took ∼2.5 h.

Impulsivity Questionnaires

We used the validated Czech translation of the Barratt scale for assessing impulsivity (57). This method includes aspects of non-planning impulsiveness, attentional impulsiveness, and motor impulsiveness. However, the three-factor structure has been questioned [e.g., (63, 64)]; therefore, only total score for this scale was calculated. Self-reported impulsivity was also measured by the Czech validated translation of the UPPS-P scale (58–60). The questionnaire consists of five subscales: Lack of premeditation (11 items), Lack of perseverance (10 items), Sensation seeking (12 items), Negative urgency (12 items), and Positive urgency (14 items), where urgency indicates the tendency to act impulsively under influence of emotions.

Behavioral Tasks

GNG Task

The GNG task contained two types of stimuli, the letter *A* was a Go stimulus and the letter *B* was a No-Go stimulus. Stimuli were in white color presented on the black screen. Subjects had to quickly react by pressing a key when letter *A* appeared and avoid the reaction when letter B appeared. A fixation cross preceded each stimulus. The whole task consisted of four blocks with 48 trials in each block. All subjects performed a short practice before the testing. The stimulus duration was 0.4 s; fixation cross duration varied from 1.1 to 2.6 s. Three parameters were analyzed from this task: No-Go commission errors percentage (percentage

TABLE 1 | Demographic, neurologic data and neuropsychological data of PD, PD-ICD and HC groups.

	PD-ICD ($n = 15$)	PD-nonICD ($n = 22$)	Healthy controls ($n = 36$)	Statistics value, p	Effect size
Gender M/F	11/4	10/12	19/17		
Age	59.27 (8.88)	69.18 (5.47)	66.14 (7.70)	$F_{(2, 70)} = 8.214$, $p = 0.001$	
Education	6.7, 13.3, 46.7, 33.4	4.5, 13.6, 68.2, 13.6	0, 16.7, 55.6, 27.7	$\chi^2_{(2)} = 0.658$, $p = 0.658$	
Socioeconomic status	6.7, 33.3, 46.7, 6.7	13.6, 22.7, 54.5, 9.0	2.8, 19.4, 52.8, 22.2	$\chi^2_{(2)} = 3.902$, $p = 0.142$	
Neurologic data					**d**
H a Y stage	2.53 (0.64)	2.48 (0.66)		$p = 0.799$, $t = 0.256$	$d = 0.085927$
Age of onset	50.80 (9.64)	62.55 (6.25)		$p < 0.001$, $t = -4.160$	$d = 1.445757$
Diseases duration	8.87 (4.17)	6.95 (4.63)		$p = 0.208$, $t = 1.282$	$d = 0.433676$
L-dopa equivalent dose	1289.75 (543.97)	1025.46 (567.18)		$p = 0.166$, $t = 1.414$	$d = 0.475602$
Neuropsychological data					η^2
MADRS	3.73 (5.68)	3.05 (3.84)	0.69 (1.83)	$F_{(2, 70)} = 5.202$, $p = 0.008$	$\eta^2 = 0.129$
SAS score	36.73 (5.40)	35.73 (5.25)	28.50 (6.59)	$F_{(2, 70)} = 14.980$, $p < 0.001$	$\eta^2 = 0.300$

Education (%), Primary, lower secondary, higher secondary, college.
Socioeconomic status (%), insufficient, unsatisfactory, satisfactory, very satisfactory.
MADRS, Montgomery Asberg Depression Rating Scale; SAS, Zung Self-reported Anxiety Scale; M, male; F, female.

of erroneous key press after No-Go trial), Go omission errors percentage (percentage of Go trials erroneously followed by no key press), and Go reaction time (average reaction time on correct Go trials). Go stimuli occurred in 83% and No-Go stimuli occurred in 17%; this ratio makes the task more cognitively demanding and the subjects prone to make more commission errors.

SST

Stimuli in the SST were white arrows pointing to the left or to the right; subjects had to press an arrow key pointing to the same direction as the arrow presented on the black screen. However, the subjects had to stop their reaction and press no key when the stimulus was followed by a visual stop signal (the arrow turned red). Stop signals appeared in 25% of trials. Delays in the presentation of stop signal (stop signal delay, SSD) varied during the task in order to prevent the subject from developing response pattern, the starting latency was 200 ms. When the subject succeeded in the trial, the latency increased by 45 ms; when the subject failed, the latency decreased by 45 ms. Each stimulus lasted until the subject reacted by pressing a key or for 1 s if there was no reaction from the subject. A fixation cross appeared before every stimulus; the duration of the cross was again variable between 1.1 and 2.6 s. The task consisted of four blocks with 48 trials in each block; a short practice preceded the testing procedure. The SSRT was calculated by subtracting the average SSD from the average Go reaction time. SSRT refers to the time that the subject needs to stop his/her reaction; the longer time needed, the more difficult it is to interrupt one's own actions; i.e., higher SSRT is linked with higher impulsivity.

DD

In the DD task, subjects were asked to choose between two possible rewards in every trial—a smaller but immediate reward or higher but delayed reward. For example, *Would you prefer to receive 510 CZK today or 990 CZK in a week?* There were five possible delays—1 day, 1 week, 1 month, 3 months, and 6 months—and two delayed reward levels 990 CZK (around 40 EUR) and 24900 CZK (around 980 EUR). These delays and rewards were set according to the pilot study. Questions with different combinations of delays and delayed rewards were presented in random order and the subject was asked if he or she prefers the immediate or the delayed reward. The amount of immediate reward varied in intervals of 20 CZK (in case of smaller delayed reward) or 500 CZK (in case of bigger delayed reward) until an indifference point, where the subjective value of the immediate reward is equal to the subjective value of the delayed reward, was found.

Two parameters were calculated for each delayed reward (k parameter and area under the curve). The hyperbolic discount parameter (k) was calculated by the equation $DR = I/(k^*D)$, where DR is delayed reward, I is immediate reward, and D is delay. Naturally, as the reward delay increases, the subjective value of this reward decreases (65). Larger values of k indicate steeper decline of the subjective value and therefore greater impulsivity. The second parameter was the area under the curve; the curve is estimated by the connection of indifference points for each delay reward. The lower the AUC means the steeper discounting and the higher impulsive choice (66).

IGT

The computerized version of IGT consisted of 200 trials (67, 68). In every trial, subjects had to make a series of choices between four card decks by pressing the key with number of the chosen deck. Two of the decks are disadvantageous (A and B) and two decks are advantageous (C and D). Subjects were informed that some of the decks were better than the other and they were instructed to play until the game ends and try to win as much money as possible. However, participants didn't know which decks are bad or good, how many trials had the game, or risk of losses in each deck. Impulsive behavior is associated with decks A and B. Deck A contains high immediate rewards with high risk of loss, and deck B contains high immediate rewards with low

TABLE 2 | Descriptive statistics of dependent variables and results of ANOVAs comparing PD-nonICD, PD-ICD, and HC groups.

	PD-ICD ($n = 15$)	PD-nonICD ($n = 22$)	Healthy controls ($n = 36$)	Statistic value, p	Effect size
Barrat scale	60.47 (7.54)	54.14 (5.60)	54.31 (6.48)	$F_{(2, 70)} = 5.537$, $p = 0.006$	$\eta^2 = 0.137$
UPPS-P PRE	20.60 (5.05)	19.77 (4.36)	18.67 (4.03)	$F_{(2, 70)} = 1.162$, $p = 0.319$	$\eta^2 = 0.032$
UPPS-P PER	20.33 (5.08)	19.14 (3.58)	16.83 (3.48)	$F_{(2, 70)} = 5.140$, $p = 0.008$	$\eta^2 = 0.128$
UPPS-P SS	22.07 (6.78)	23.64 (6.76)	26.25 (6.85)	$F_{(2, 70)} = 2.317$, $p = 0.106$	$\eta^2 = 0.062$
UPPS-P NU	27.27 (6.44)	25.18 (6.54)	25.51 (6.22)	$F_{(2, 69)} = 0.537$, $p = 0.587$	$\eta^2 = 0.015$
UPPS-P PU	28.33 (7.51)	28.27 (6.99)	26.69 (8.25)	$F_{(2, 70)} = 0.391$, $p = 0.678$	$\eta^2 = 0.011$
Go omissions %	18.95 (5.57)	18.76 (7,80)	16.94 (5.96)	$F_{(2, 70)} = 0.782$, $p = 0.461$	$\eta^2 = 0.022$
Go RT	419.36 (50.98)	418.03 (48.11)	402.83 (56.48)	$F_{(2, 70)} = 0.808$, $p = 0.450$	$\eta^2 = 0.023$
No-Go commissions %	18.65 (12.36)	25.97 (19.51)	22.45 (17.21)	$F_{(2, 70)} = 0.827$, $p = 0.442$	$\eta^2 = 0.023$
SSRT	298.46 (125.45)	242.36 (115.86)	281.97 (80.90)	$F_{(2, 69)} = 1.580$, $p = 0.213$	$\eta^2 = 0.044$
DD k 990	0.022 (0.046)	0.061 (0.125)	0.019 (0.050)	$F_{(2, 65)} = 1.886$, $p = 0.160$	$\eta^2 = 0.026$
DD k 24900	0.005 (0.0103)	0.077 (0.385)	0.004 (0.005)	$F_{(2, 69)} = 0.626$, $p = 0.538$	$\eta^2 = 0.018$
DD AUC 990	0.61 (0.31)	0.43 (0.29)	0.58 (0.34)	$F_{(2, 68)} = 1.854$, $p = 0.164$	$\eta^2 = 0.052$
DD AUC 24900	0.76 (0.25)	0.71 (0.23)	0.76 (0.30)	$F_{(2, 68)} = 0.251$, $p = 0.779$	$\eta^2 = 0.007$
IGT NET score 1st part	13.80 (29.33)	3.18 (25.80)	7.17 (25.28)	$F_{(2, 70)} = 0.729$, $p = 0.486$	$\eta^2 = 0.020$
IGT NET score 2nd part	39.07 (44.89)	−0.91 (33.84)	15.00 (37.43)	$F_{(2, 70)} = 4.925$, $p = 0.010$	$\eta^2 = 0.123$
IGT B % 1st part	24.55 (9.03)	32.55 (10.72)	31.00 (11.27)	$F_{(2, 70)} = 2.723$, $p = 0.073$	$\eta^2 = 0.072$
IGT B % 2nd part	16.86 (13.74)	36.64 (17.04)	30.58 (15.98)	$F_{(2, 69)} = 6.696$, $p = 0.002$	$\eta^2 = 0.163$
Digit span	14.47 (2.72)	14.18 (3.00)	14.67 (3.87)	$F_{(2, 68)} = 0.138$, $p = 0.872$	$\eta^2 = 0.004$
d2 speed	119.07 (24.99)	106.80 (24.50)	126.06 (19.99)	$F_{(2, 66)} = 4.624$, $p = 0.013$	$\eta^2 = 0.123$
d2 accuracy (error %)	9.25 (8.78)	8.67 (6.06)	9.39 (6.21)	$F_{(2, 66)} = 0.074$, $p = 0.929$	$\eta^2 = 0.002$
ToL moves	34.79 (17.08)	40.90 (24.29)	31.08 (19.67)	$F_{(2, 68)} = 1.493$, $p = 0.232$	$\eta^2 = 0.042$
ToL init. time	137.21 (71.74)	91.25 (42.32)	109.81 (55.98)	$F_{(2, 68)} = 2.841$, $p = 0.065$	$\eta^2 = 0.077$
ToL exec. time	337.71 (164.86)	360.10 (175.52)	278.33 (141.59)	$F_{(2, 68)} = 2.000$, $p = 0.143$	$\eta^2 = 0.056$

PRE, Lack of premeditation; PER, Lack of perseverance; SS, Sensation seeking; NU, Negative urgency; PU, positive urgency; Go RT, Go reaction time; SSRT, Stop signal reaction time; DD, delay discounting; AUC, Area under the curve; IGT, Iowa gambling task; IGT B %, percentage of B deck cards selections; ToL, Tower of London; moves, total number of moves made during the task; ToL inic. time; ToL exec. time.

risk of very high loss. IGT net score was calculated by subtraction of disadvantageous deck choices from advantageous deck choices [(C + D) − (A + B)]. We also compared the relative frequency of A and B deck choices.

Cognitive Abilities and Executive Functions

For working memory, the total score of Digit span subtest from WAIS-III (69) was analyzed. Three parameters from Tower of London (70) were calculated for assessment of executive functions—total move score, total initiation time, and total execution time. Attention was measured by test d2-R (71) with two analyzed parameters—speed (total number of processed items) and accuracy (percentage of omission and commission errors).

MRI Data Acquisition and Analysis

After the behavioral testing, the patients and controls underwent MRI scanning. Ten patients and eight controls did not undergo the acquisition due to MRI contraindications or inability to tolerate the procedure. The scanning was performed using a 3-T MRI scanner, SIEMENS MAGNETOM Prisma syngo (Siemens Medical Systems, Erlangen, Germany) at the Central European Institute of Technology of Masaryk University, Brno, Czech Republic. A high-resolution T1-weighted scan was acquired using the following parameters: MPRAGE sequence with repetition time = 2,300 ms, echo time = 2.34 ms, flip angle = 8°, voxel size 1.00 × 1.00 × 1.00 mm, matrix 240 × 224 × 224. Further three patients were excluded from the scanning because of excessive head movement resulting to significant motion artifacts not compatible with the automatic processing pipeline. The final size of the sample that competed MRI session was 16 PD-nonICD patients, 8 PD-ICD patients, and 28 healthy controls.

Volumetric segmentation was performed in this T1-weighted scan using the standard automated pipeline (72) implemented in the FreeSurfer image analysis suite, version 5.3.0 (http://surfer.nmr.mgh.harvard.edu/). The accuracy of the segmentation in each subject was visually inspected by a trained operator (P.F.). The volumes (adjusted for the estimated intracranial volume) and surface areas (in case of cortical regions) of several regions of interest (**Table 3**) and the volume of the whole brain, as provided by the automatic segmentation algorithm of FreeSurfer, were compared between the PD-nonICD, PD-ICD patients and healthy controls using one-way analysis of variance (ANOVA) with Bonferroni *post-hoc* multiple-comparison correction.

We performed statistical comparisons (two-sample *t*-tests) of subgroup of patients who underwent MRI scanning with the subgroup of patients who did not undergo MRI scanning to be

TABLE 3 | Anatomical regions of interest.

Anatomical region	Side
Caudate	R,L
Putamen	R,L
Nucleus accumbens	R,L
Accumbens area	R,L
Caudal anterior cingulate	R,L
Rostral anterior cingulate	R,L
Caudal middle frontal	R,L
Rostral middle frontal	R,L
Lateral orbitofrontal	R,L
Medial orbitofrontal	R,L
Pars orbitalis	R,L
Pars triangularis	R,L
Precentral gyrus	R,L
Insula	R,L

L, left; R, right.

sure that the MRI subgroup was not significantly different from the original patient group in the behavioral, demographic, and other measured parameters.

Statistical Analysis

Data were analyzed in IBM SPSS Statistics 24 software. We compared demographic characteristics, performance in computerized tasks, cognitive tasks, scores from questionnaires, and MRI parameters between groups of healthy controls, Parkinson patients with ICD, and Parkinson patients without ICD. The data from computerized behavioral tasks, questionnaires, and cognitive tasks were compared by one-way ANOVA without covariates. In cases of significant group differences, Tukey's *post-hoc* tests were applied. Sociodemographic characteristics (education, socioeconomic status) were analyzed by Kruskal–Wallis *H*-test; neurological data of the two patient groups were analyzed by independent *t*-tests. IGT net scores of the first and the second part of the task were analyzed in *jamovi* software by repeated measures ANOVA with Tukey's *post-hoc* tests with time (first vs. second part of the task) as within-subject factor and group as between-subject factor. Results are reported at $p < 0.05$ level of significance.

RESULTS

Demographic Data

The three groups did not differ in education or socioeconomic status (**Table 1**). The groups were also matched by age; the healthy controls were selected to have similar age to patients with 2 years tolerance. However, there was a difference in age between groups; patients with ICD were significantly younger than those without ICD and healthy controls (PD-nonICD vs. PD-ICD: $p < 0.001$, PD-ICD vs. HC: $p = 0.009$). The PD-ICD patients were younger than PD-nonICD patients at the time of the disease onset (PD-ICD vs. PD-nonICD: $p < 0.001$). There were no differences in disease duration, levodopa equivalent dose, or Hoehn and Yahr stage between clinical groups.

The group of patients who underwent MRI scanning did not differ from the group of patients without MRI in the cognitive abilities, behavioral parameters, or self-reported impulsivity. However, the groups significantly differed in age ($p = 0.028$, group with MRI mean = 67.56, $SD = 6.4$; group without MRI mean = 58.7, $SD = 10.5$).

Depression and Anxiety

There was a significant effect of group on scores of anxiety and depression. Both clinical groups (PD-ICD and PD-nonICD) had higher scores of depression than healthy controls (MADRS score PD-ICD vs. HC: $p = 0.018$, PD-nonICD vs. HC: $p = 0.043$). Both clinical groups also had significantly higher levels of anxiety than healthy controls (SAS score PD-ICD vs. HC: $p < 0.001$, PD-nonICD vs. HC: $p < 0.001$). No significant differences were detected between PD-nonICD and PD-ICD patients in anxiety or depression.

Impulsivity Questionnaires

There were significant group differences in the Barratt scale score. The PD-ICD group scored the highest on the Barratt scale, which means that PD-ICD patients were more impulsive than PD-nonICD patients ($p = 0.013$) and controls ($p = 0.008$). The PD-nonICD group and control group did not differ in the Barratt scale score ($p = 0.995$). In the UPPS-P scale, patients with ICD showed elevated score, as compared to healthy controls, in Lack of perseverance ($p = 0.017$). No differences between the groups were found in the other UPPS-P subscales. The PD-nonICD group did not differ from healthy controls in any of the self-reported impulsivity measurements and did not differ from PD-ICD except for the Barratt scale score.

Behavioral Tasks

There was no significant effect of group on performance in GNG, DDT, or SST (**Table 2**). Both groups of patients had similar RTs, accuracy, SSRT, and discounting parameters as healthy controls. Group differences were found in performance in IGT. Analysis revealed significant effects of time, group, and time vs. group interaction on the IGT net score [(C + D) − (A + B)]. There were no significant differences in the NET score in the first part of the task, but the PD-ICD group had significantly higher NET score than the PD-nonICD group ($p = 0.007$) in the second part of the task. No significant differences were found between healthy controls and PD-nonICD or between healthy controls and PD-ICD. There was significant effect of time vs. group interaction [$F_{(2, 70)} = 3.36$, $p = 0.041$]. *Post-hoc* tests revealed that only the PD-ICD group improved their NET score in the second half of the task; the difference was marginally significant in PD-ICD ($p = 0.055$) and not significant in other groups (HC: $p = 0.733$, PD-nonICD: $p = 0.993$). We further made analysis of particular deck selections in the first and second half of the task. There was a group difference in B deck preference in the second half of the task; specifically, the PD-ICD group selected cards from the B deck less likely than the PD-nonICD group (PD-ICD vs. PD-nonICD: $p = 0.002$) and healthy controls (PD-ICD vs. HC:

$p = 0.021$). No significant differences were found in A deck selection relative frequency.

Cognitive Abilities and Executive Functions

The three groups did not differ in working memory (Digit span). ANOVA revealed significant group differences in processing speed in d2 test. Patients without ICD were significantly slower than healthy controls (PD-nonICD vs. HC: $p = 0.009$). No significant differences were found between the PD-ICD patients and healthy controls or between the two patients' groups in the accuracy in d2 test. No significant differences were detected in total move score and total execution time in the Tower of London. However, we observed a trend in total initiation time between the PD-nonICD and PD-ICD group. The PD-ICD group showed longer incitation time than PD-nonICD group, but the comparison was only marginally significant (PD-nonICD vs. PD-ICD $p = 0.052$). All groups worked with similar accuracy in the test.

MRI

PD-nonICD patients differed from HC in the estimated intracranial volume (eICV) of the right nucleus accumbens area ($p = 0.002$), bilateral pars orbitalis ($p < 0.001$), the left pars triangularis ($p = 0.002$), and the left precentral gyrus ($p = 0.032$) (**Table 4**); PD-nonICD patients showed decrease of volumes in all of these regions (All presented p-values are Bonferroni-corrected for multiple comparisons.) PD-nonICD patients also showed cortical thinning of the left pars orbitalis ($p = 0.020$) in comparison with HC. PD-ICD patients in comparison with HC showed increase of the right caudal anterior cingulate area ($p = 0.003$) and right rostral middle frontal area ($p = 0.018$) and also increase of total volumes of these regions (right caudal ACC, $p = 0.010$, right rostral middle frontal $p = 0.007$). However, differences in eICV volumes in these areas did not reach significance in the case of PD-ICD group. Both groups—PD-nonICD and PD-ICD—showed a decrease in the eICV volume of the right precentral gyrus in comparison with HC, but none of the results reached significance in *post-hoc* testing ($p > 0.05$). In the comparison of PD-nonICD and PD-ICD, only total volumes of bilateral pars orbitalis (right $p = 0.029$, left $p = 0.039$) and right caudal anterior cingulate ($p = 0.041$) differed, with PD-ICD patients having greater volumes. Comparison of cortical areas, eICV volumes, or cortical thickness between the two patient groups did not bring any significant results.

TABLE 4 | Results of anatomical structures comparisons—significant contrasts.

Volumes	*p*	*F*	Significant contrasts
Right accumbens area	0.022	4.130	PD-nonICDxHC
lh pars orbitalis	0.013	4.737	PD-nonICDxHC, PD-nonICDXPD-ICD
rh caudal anterior cingulate	0.012	4.850	PD-nonICDXPD-ICD, PD-ICDxHC
rh pars orbitalis	0.005	5.841	PD-nonICDXPD-ICD, PD-nonICDxHC
rh rostral middle frontal	0.009	5.202	PD-ICDxHC
Volumes eICV			
Right accumbens area	0.003	6.688	PD-nonICDxHC
lh pars orbitalis	0.000	10.515	PD-nonICDxHC
lh pars triangularis	0.002	7.074	PD-nonICDxHC
lh precentral gyrus	0.013	4.718	PD-nonICDxHC
rh pars orbitalis	0.000	13.144	PD-nonICDxHC
rh precentral gyrus	0.021	4.160	No significant contrast
Thickness			
lh pars orbitalis	0.021	4.171	PD-nonICDxHC
Area			
rh caudal anterior cingulate	0.005	6.006	PD-ICDxHC
rh rostral middle frontal	0.022	4.146	PD-ICDxHC

Volumes eICV, estimated intracranial volume; lh, left hemisphere; rh, right hemisphere.

DISCUSSION

In the study, several possible factors associated with ICD were compared across the groups (anxiety, depression, age, age of onset, disease stage, and duration). Among these factors, only age of onset and age differed between the ICD and non-ICD group. Patients with ICD were younger and had lower age of disease onset than patients without ICD. Our results support previous research reporting association between PD-ICD and younger disease onset or younger age (2, 11–14).

Elevated self-reported impulsivity in the Barratt scale in PD-ICD in comparison with HC and PD-nonICD is consistent with previous research in this population (9, 10, 13, 73). In the UPPS-P scale, our results did not confirm our hypothesis regarding elevated Sensation seeking in PD-ICD. The absence of differences in Sensation seeking in PD-ICD might be surprising, when some other studies found associations of higher Sensation/Novelty seeking with ICD in this population (7–9, 13) [but see Evans et al. (12)]. The differences might be due to using various measurement tools with different concepts of Sensation seeking. Regarding the UPPS-P dimensions, we found only one study that targeted these dimensions in PD-ICD (7). This work reported increased impulsivity in Lack of premeditation, Urgency, and Sensation seeking in PD-ICD in contrast with HC and elevated Sensation seeking in contrast with PD-nonICD patients. However, only the shortened 16-item UPPS scale was used and the scale was answered by close relatives of the patients not the patients themselves, which may cause inconsistency of their results with our findings. PD-ICD patients in contrast with HC showed elevated score only in the Lack of perseverance. Perseverance is defined as "the ability to remain focused on a task that may be boring and/or difficult." Lack of perseverance has been associated with poor resistance to distraction, harm avoidance, poor concentration on boring or difficult tasks, lower responsibility perception, and difficulties in dealing with frustration (74). Lower perseverance was reported in people with obsessive–compulsive symptoms, compulsive buying (74–77), bulimia (78), and self-injury behavior (79). One study found lower perseverance in PD patients with and without ICD (7). PD-ICD patients in our sample did not manifest higher levels of Urgency, which represents the aspect of emotional impulsivity. Taken together with no impairments in impulsive choice, it seems

that impulsivity in PD-ICD is not elevated by strong emotions unlike, for example, borderline disorder, where impulsivity is more prominent in intense emotional state (6, 80, 81). PD-ICD patients are more likely to avoid harm and lower their effort in boring or difficult situations. They have impaired ability to maintain long-term goal and facing the obstacles; when facing difficulties, they rather abandon the goal. Even though UPPS-P questionnaire is the most up-to-date personality model of impulsivity, it is not used in studies conducted on PD-ICD populations. Future research with larger sample sizes studying PD-ICD in the context of UPPS-P impulsivity model would be beneficial.

In accordance with our hypothesis, PD-ICD patients in our study did not show impairments in impulsive action (waiting and stopping impulsivity). Results were also negative for the non-impulsive group. Previous studies of impulsive action in general PD population brought mixed results (38–44). There might be several factors responsive for the inconsistency in impulsive action among studies. Differences in results can be caused by cognitive impairments in patients' groups, heterogeneity in the patients' samples, and by differences in task designs. Patients in studies have different clinical characteristics such as different disease stage and duration, cognitive impairments, and different severity of anxiety and depression. Some of the studies included patients with cognitive impairments and elevated depression in their samples (38, 45). Presence of cognitive deficits and depression were linked to lower efficacy of inhibitory performance in impulsive action tasks (38, 82). Further, patients with older age and later disease stages have greater difficulties when inhibiting their responses (38). Thus, it is possible that increased impulsive action observed in some studies in the previous literature might have been influenced more by impaired cognitive functioning or psychomotor slowing associated with markedly increased depression, rather than with increased impulsivity itself.

We expected elevated choice impulsivity in PD-ICD in comparison with healthy controls, but our results did not support this expectation. None of the clinical groups differed from healthy controls on Delay discounting. Unimpaired performance of PD-ICD patients on Delay discounting is in contrast with two studies (9, 24), which found elevated discounting in PD patients with ICD in comparison with HC and non-impulsive PD patients. However, PD-ICD patients in these studies had either lower IQ or working memory deficits or were more depressed than non-impulsive patients. All of these factors were previously associated with greater discounting (83–86). Consistently with our findings, another study (28) reported similar delay discounting comparing PD-ICD and HC. The results of DD studies in PD-ICD population remain inconsistent. It is again possible that presence of cognitive impairments or elevated depression could influence performance in this task in previous studies. Future research should focus on relationship of depression, cognitive deficits, and behavioral measures of impulsivity in this population.

In the IGT in our study, patients with ICD performed surprisingly the best from all groups. PD-ICD as the only group improved their performance in the second part of the task and made significantly less risky choices. PD-ICD patients differed from PD-nonICD and HC in B deck card preference. B deck is a deck with low frequent but very high losses and high frequent gains. This deck is disadvantageous in long-term outcome. Therefore, according to the basic IGT assumption, the frequency of B deck choice declines during the task in a healthy population (67). This basic IGT assumption is being questioned, since the high preference of B deck choices observed in a healthy population in many studies suggests that it is rather the gain–loss frequency than the long-term outcome that influences decision-making in IGT in a healthy population (87). Our results suggest that PD-ICD patients, unlike HC and patients without ICD, are less sensitive to gain-loss frequency and more sensitive to high punishments. Previous studies brought evidence of impaired IGT performance in PD patients (ICD not specified) (16–23, 88) and in pathological gamblers with Parkinson (25). The difference between our study and that of Rossi et al. (25) is that we also included other forms of ICD beside pathological gambling. We recruited some patients with gambling history into our sample. It is possible that these patients with gambling history were more aware of potential risk because of their previous problems and they already developed some strategies, which helped them during the task. In contrast with previous studies, we used a prolonged protocol consisting of 200 trials. The differences between groups were more prominent in the second part of the tasks where PD-ICD patients chose the cards from the disadvantageous deck less frequently than in the first part. It seems that this prolonged version is more sensitive to describe learning from the consequences of the traditional 100 card version. We further analyzed not only the NET score but also the preference of particular packages. This four-deck approach seems to be useful, because it provides more information about decision strategies of participants.

Having in mind the age differences between groups of patients in our study, the role of age in the context of IGT results should be considered. PD-ICD in our study performed better than PD-nonICD, and they were also younger than PD-nonICD patients. Biars et al. (29) reported that increasing age negatively influenced IGT performance. Some studies found older adults to have greater tendency to less advantageous decisions in IGT than younger adults (89, 90). It is possible that older adults use different cognitive strategies and are not able to learn from the feedback as effectively as younger adults (89). On the other hand, studies reporting impaired performance in the PD or PD-ICD group in IGT found no significant age differences between compared groups (16, 18, 20–22, 25). Further investigation in this field would be beneficial.

As for cognitive functions, patients did not show any significant impairments except slower processing speed in the d2 test in PD non-ICD in contrast with HC. It may be surprising, because a decline of cognitive functions is linked to PD and cognitive impairment was previously find in patients with ICD (5). However, only patients with high MMSE scores were recruited, and therefore, those with potential cognitive problems were excluded from the testing. The slower processing speed of PD-nonICD patients in contrast to HC in d2 can be attributed to age, because the PD-nonICD group was the oldest one. Slower

processing speed can also indicate attentional problems. It is possible that PD-nonICD patients are able to complete the task with similar accuracy as other experimental groups, but it costs them more effort; as a result, they need more time to process the same amount of items.

Although there were no impairments in PD-ICD on behavioral tasks, MRI scanning revealed structural differences between the three groups in the structures involved in inhibitory control and decision making. PD-ICD patients showed volume increase of ACC in comparison to PD patients and healthy controls. Our results correspond with previous research, which found increased thickness of ACC cortex in PD-ICD (48, 49, 51). Decreased functional connectivity of ACC with nucleus accumbens was previously associated with impulsive–compulsive behavior in PD (51). ACC is an important component of the reward system. It is involved in subjective evaluation of immediate and delayed rewards in delay discounting (91). Some researchers suggest that this structure is also important for conflict monitoring in situations with low predictability and high error rate; when the subject is required to adjust behavior after error response, it is needed for learning from the negative feedback (49, 92). Considering an increase in ACC volume together with the improvements in PD-ICD group during the second part of the IGT task, it suggests that PD-ICD patients were the most sensitive to the negative feedback. PD-ICD patients in our study showed an increase of volume and area in the right rostral middle frontal region in comparison with HC. Middle frontal region abnormalities in PD-ICD population were previously reported Biundo et al. (47) and Yoo et al. (50), who observed cortical thinning in PD-ICD. Increased activity of the right middle frontal gyrus was previously observed during impulsive action tasks (93). This region is associated with working memory, norm- or rule-related behavior, and making strategic decisions in social context (94, 95).

However, our results are not entirely consistent with previous research. One study of PD-ICD patients reported no structural differences between PD-ICD and PD-nonICD or HC (96). Recent research brought also evidence of structural differences in orbitofrontal cortex and nucleus accumbens in PD-ICD (47–49), but our group comparisons were negative regarding these regions. Differences in anatomical findings across the studies might be caused by different analysis approaches and further by the presence of cognitive impaired individuals in some of the studies, as well as by variability of ICD patients in behavioral manifestations of ICD, in disease duration and disease progression. Disease progression and symptom severity are very important factors. For example, PD-ICD patients in the study of Pellicano et al. (48), which observed more extensive structural changes than our study, were in more advanced stage and showed more severe disease symptoms than non-impulsive patients. On the other hand, the study of Ricciardi et al. (96), which did not find any structural differences, included patients in earlier stage of the disease and with shorter disease duration than our study. Some studies tested patients with mild cognitive impairment (47, 49). Most of the studies included patients with variable ICD symptoms often with more than one manifestation of ICD. We also included variable ICD sample into our study. It is possible that particular subtypes of impulsive behavior like gambling, hypersexuality, or binge eating differ from each other in behavioral impulsivity or in their neurobiological correlates.

Patients without ICD differed from healthy controls in the regions of inferior frontal gyrus, right nucleus accumbens, and left precentral gyrus. These findings also indicate that patients without ICD have some brain pathology in regions relevant for impulsivity. This corresponds with previous MRI research conducted on the general PD population (42, 97–100).

This study has several limitations. First of all, the research sample consisted of a small number of patients due to the inclusion of only patients with severe impulsive problems and avoiding patients with cognitive deficit. Even though the prevalence of ICD in the population is higher, we decided to include only patients with severe ICD, which has a truly observable effect on their day-to-day life (e.g., substantial financial losses due to gambling). We deliberately decided to exclude patients with subclinical or borderline behavioral problems, because PD patients often manifest with a variety of behavioral problems, but only problems that differ from premorbid level of everyday functioning should be considered as a disorder. Hence, the inclusion of borderline patients would affect the validity of the study.

Secondly there is heterogeneity in our patient sample—we included patients with various manifestations of ICD. Future research studies could separately analyze individual subtypes of PD-ICD. Another limitation is the age difference between the PD-ICD and PD non-ICD patients. This factor needs to be considered, and caution should be exercised in interpretation of group differences. Moreover, not all of our patients were able to successfully undergo MRI testing; therefore, the sample for MRI testing was smaller than the sample for behavioral testing. However, the statistical comparison did not find any differences in self-reported impulsivity and behavioral performance between the subgroup of patients who underwent the MRI assessment and the group of patients without MRI testing. The last factor that may have influenced the results was the presence of some patients with a history of ICD. It is possible that previous personal experience could influence the behavior of these patients during the testing.

CONCLUSION

The discrepancy between the presence of florid ICD signs, both in clinical follow-up and in self-reported impulsivity scales, and the comparable or even better performance of PD-ICD patients in rather well-established behavioral tasks is rather intriguing. This stalemate is further accentuated by significant structural differences in various neural nodes related to inhibitory control and reward processing in PD-ICD patients. Be it the lack of sensitivity in specific, limited ICD subtypes, excessive caution of ICD patients due to previous negative experience rendering simplistic tasks insufficient, or other, as of now unknown aspects, the issue of impulsivity in PD definitely warrants further research, ultimately to allow proactive prevention of this debilitating complication of PD.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Etická komise Masarykovy univerzity. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PH, PF, PL, MS, MBal, MBar, and TK participated in designing the project and defining the aims and hypotheses. PF, RŠ, MBal, and MBar were responsible for patient recruitment and neurological examinations. PH and PL performed neuropsychological testing. PH and PF performed the data analysis and wrote the manuscript draft. All co-authors provided their comments to the manuscript draft.

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Annex 5

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Behavioral inhibition in neutral and emotional contexts in acutely violent patients with schizophrenia spectrum disorders

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Abstract

Reduced impulse control and emotion dysregulation are associated with an increased risk of violence in psychosis. We used an emotional stop-signal task (ESST) with angry and neutral facial expressions stimuli to examine the differences in inhibition in neutral and emotional contexts between acutely violent ($N=117$) and non-violent ($N=50$) patients with schizophrenia spectrum disorders and healthy volunteers ($N=50$). However, 66 violent patients (56.41%) from the final sample with a higher level of self-reported impulsivity did not finish the behavioral task. Inhibition was found to be weaker in emotional than in neutral contexts in both the violent ($n=51$) and non-violent patient groups in comparison with healthy controls. At the same time, violent patients had weaker inhibition in both neutral and emotional contexts than non-violent patients and healthy controls. Violent patients also showed significant associations between response inhibition and positive schizophrenia symptoms. These results show that emotion regulation impairment is present in schizophrenia patients in general and violent behavior is associated with higher impulsivity regardless of the emotional context. Impaired response inhibition seems to be a stronger indicator for violent patients than the disorder itself, and it may constitute a marker for the risk of violent behavior in psychotic patients. Positive symptoms might fall into underlying factors of increased impulsivity in acutely violent psychotic patients. However, the emotional stop-signal task seemed to be too strenuous for highly impulsive patients and acutely violent patients with psychosis, and its use was limited to the patients who were able or willing to complete the task.

Keywords Emotional stop-signal task · Response inhibition · Emotion regulation · Schizophrenia spectrum disorder · Violence

Introduction

Aggressive behavior constitutes a frequent and heterogenous problem in patients with psychotic disorders (Černý et al., 2018; Nichtová et al., 2020; Whiting et al., 2022). Impulsivity and impulsive aggression are one of the etiological subtypes of violent behavior in schizophrenia patients (Volavka & Citrome, 2008). Schizophrenia patients exhibit impulsive behavior that is apparently based on inadequate response inhibition (Stahl, 2014). Reduced impulse control is associated with an increased risk of violence in psychosis (Hoptman, 2015; Nolan et al., 2005) and is often linked to emotion dysregulation. Increased susceptibility to emotional triggers in combination with poor response inhibition is an important underlying factor of aggression in patients in acute stages of psychosis (Krakowski et al., 2016).

Impaired response inhibition in schizophrenia patients was associated with high aggression; response inhibition

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was higher in angry trials than in neutral trials (Pawliczek et al., 2013). Patients also showed lower accuracy in neutral trials than healthy controls did; patient performance in angry trials was similar to that of healthy controls (Pawliczek et al., 2013; Pessoa et al., 2012). Thus, it seems that psychotic symptoms undermine impulse control mainly in neutral situations. Overall, aggressive behavior in schizophrenia patients seems to be underlined by deficits in both impulse control and emotion regulation, and psychosis leads to deficits in both critical areas.

Another deficit in schizophrenia patients associated with the propensity to violence is impaired facial emotion recognition (Bulgari et al., 2020). Violent schizophrenia patients, compared to non-violent ones, showed significantly weaker performance in facial recognition on all emotions, with even more severe impairment in negative emotions such as anger or fear (Bulgari et al., 2020). Despite the clear involvement of both impulsivity and emotion regulation in aggression in schizophrenia, few studies have used emotional impulsivity tests in schizophrenia research (Herbert & Sütterlin, 2011; Vercammen et al., 2012), or more specifically tests with facial stimuli (Derntl & Habel, 2017; Egashira et al., 2015; Pinkham et al., 2011).

In this study, we examined the differences between a group of violent and non-violent patients with schizophrenia spectrum disorders and healthy controls in behavioral response inhibition in neutral and emotional stimuli. For this purpose, we used an emotional variant of the stop-signal task (Pawliczek et al., 2013), an established and widely used measure of response inhibition that estimates the time needed for stopping one's unwanted actions (stop-signal reaction time; SSRT). The slower the SSRT, the harder it is to inhibit one's actions and the higher the impulsivity. As stimuli, we used pictures of human faces to reflect the aspect of impaired emotional recognition in schizophrenia; the faces were either emotionally neutral or angry (emotional condition). Based on the previous literature, we hypothesized that both psychotic patient groups have impaired response inhibition in the neutral condition in comparison to healthy controls. In acutely violent patients, a negative association between self-reported impulsivity, positive symptoms, and aggression severity with SSRT was expected (Nolan et al., 2011).

Materials and methods

Procedure

The participants underwent a modified version of the stop-signal task, the emotional stop-signal task (ESST) (Pawliczek et al., 2013), which was used as a behavioral measure of impulsivity in the context of emotional facial processing. Further, the Barratt Impulsiveness Scale (BIS-11) was used as a self-reported measure. The patients who committed violent acts during hospitalization were also administered Modified Overt Aggression Scale (MOAS) to assess the type and severity of aggression and the Positive and Negative Syndrome Scale (PANSS) to assess possible underlying factors of aggressive behavior. The experiment took place in the hospital in a separate quiet room and the administration was led by a psychologist. The assessment required approximately 60 to 90 min. All respondents signed informed consent forms to participate in the study and to process the data for research purposes. The study was approved by the Ethics Committee of the First Faculty of Medicine, Charles University in Prague, and by the ethics committees of the collaborating hospitals.

Participants

The final sample consists of 117 (71 men; 60.7%) acutely violent patients with psychotic disorders hospitalized on acute psychiatric wards who behaved aggressively during their hospitalization. Participants were recruited within our previous research study dealing with the deconstruction of violence in acutely exacerbating psychotic patients (Nichtová et al., 2020) for further understanding the underlying mechanisms of violent behavior in psychotic patients (124 participants were approached to complete the behavioral task, Fig. 1). Inclusion criteria were age above 18 years, aggressive behavior during hospitalization, and an overall score higher than 4 points on the MOAS (see Measures). Patients were hospitalized on acute wards at the Psychiatric Hospital Bohnice in Prague. The Czech version of the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) was used to assess the psychotic disorder (F2x.x) among all participants. Only violent patients diagnosed with schizophrenia, delusional disorder, acute polymorphic psychotic disorder, or schizoaffective disorder based on the ICD-10 classifications (World Health Organization, 1992) were invited to participate in this study.

From the total sample, 66 individuals (56.41%) were unable or unwilling to complete even a single block of the ESST, so their data could not be analyzed. Behavioral data from participants who completed the behavioral task ($n=51$; 54% male) were compared with two control groups. The first control group were non-violent psychotic patients ($N=50$; 60% male) hospitalized at the Psychiatric Hospital Bohnice in Prague. The same diagnostic procedures were used as in the first group of patients. The inclusion criteria were age above 18 years and absence of aggressive behavior throughout the whole hospitalization (patients were tested at the end of their hospitalization). The second control group was composed of healthy volunteers ($N=50$; 48% male). The inclusion criteria were age above 18 years and no personal

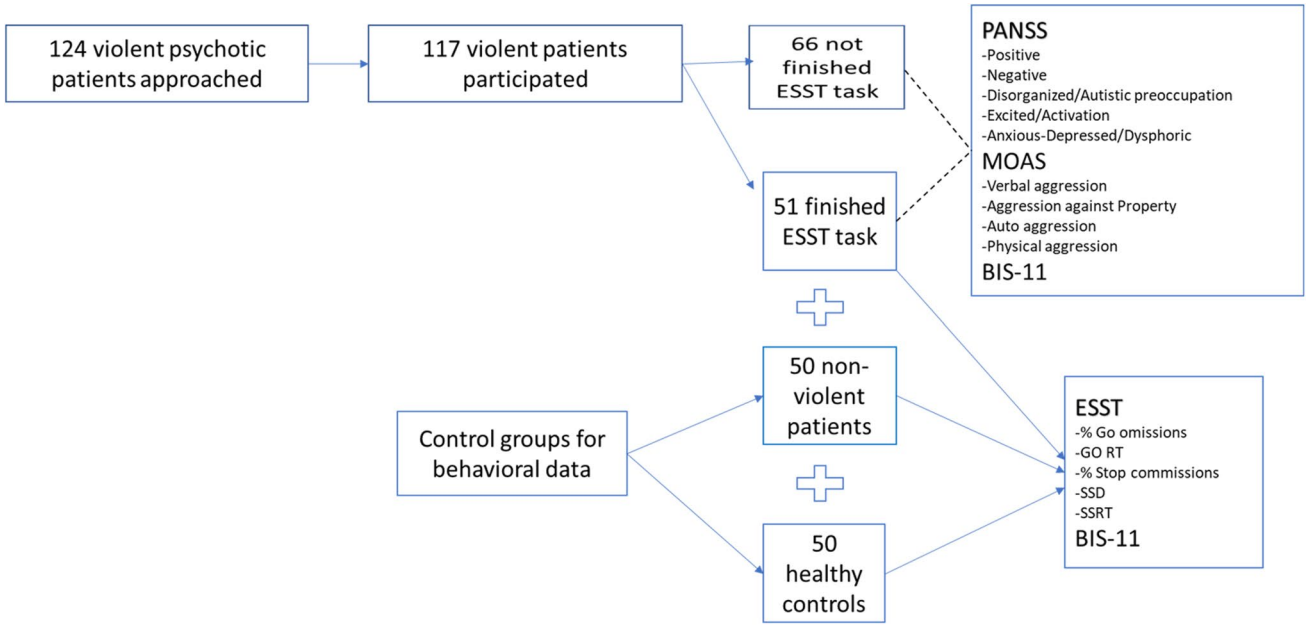

Fig. 1 Flow diagram of dataset and measures

history of mental illness. Healthy volunteers from the general population were recruited from among students, hospital employees, and their acquaintances, using a snowball method of sampling.

Measures

The *emotional stop-signal task* (ESST) (Pawliczek et al., 2013) is a behavioral method measuring the ability to inhibit a dominant motor response using emotional and neutral stimuli. As stimuli, the task uses pictures of male (50%) and female (50%) facial expressions from the Facial Emotions for Brain Activation (FEBA) set (Gur et al., 2002) displaying neutral expressions or angry expressions. In our study, each picture was surrounded by a white frame that turned yellow at unpredictable times to serve as a stop signal. The task consisted of 400 stimuli with 300 *go* trials and 100 *stop* trials divided into 4 blocks. Each trial was terminated either by a button press or after 1 s. The inter-trial interval lasted 2 s, during which the participants watched a fixation cross. Subjects were instructed to respond to pictures on the screen as fast as possible with a button press (*A* for angry faces with a left finger; *L* for neutral faces with a right finger). If a picture frame turned yellow, the participants were instructed to withhold their reaction (a *stop* trial). Thus, the *go* process starts with the presentation of the trial while the *stop* process starts with the stop signal delay (SSD) based on the independent race model (Logan & Cowan, 1984). The SSD started at 200 ms (ms) and varied from one *stop* trial to the next according to the staircase procedure. After each successful response inhibition, the SSD increased by 64 ms, making it more difficult to inhibit the reaction in the next *stop* trial; after each failed response inhibition, the SSD decreased by 64 ms, making it easier to inhibit the reaction in the next *stop* trial (Derntl & Habel, 2017). The stop-signal reaction time (SSRT) is the main outcome of the task and constitutes the individual estimated time needed to stop one's reaction. A higher SSRT indicates a more difficult inhibition and higher impulsivity. SSRT was estimated for each subject according to the integration method (Verbruggen et al., 2019). As additional outcomes, *go* omissions percentage, *go* reaction times, *stop* commissions percentage, and SSD were computed for *go* and *stop* trials in angry and neutral conditions.

The Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995) was used as a self-report questionnaire assessing different facets of trait impulsivity. BIS-11 is composed of 30 items describing common impulsive or non-impulsive (reverse-scored items) behaviors and preferences on a 4-point Likert scale. Higher scores indicate higher impulsivity; the total score was used.

The semi-structured Modified Overt Aggression Scale (MOAS; Kay et al., 1988) was used in the group of violent psychotic patients as an inclusion measure and as a measure of the type and severity of aggressive acts (Nichtová et al., 2020). The rating scale contains four categories: verbal aggression, aggression against property, auto-aggression, and physical aggression. MOAS was evaluated after the first violent incident.

In the group of violent patients, schizophrenia symptom severity was evaluated with the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). The PANSS is divided into 5 factors: positive, negative, disorganized/autistic preoccupation, excited/activation, and anxious-depressed/dysphoric (Lindenmayer et al., 1994). If a symptom measured by the item is absent, it is scored as 1; the rating points of 2 to 7 correspond to incremental levels of symptom severity.

Statistical analysis

Data were analyzed using statistical software IBM SPSS Statistics 27.0 (IBM Corp., Armonk, NY, USA), Jamovi 1.6.3 (the jamovi project, 2021, Available at: https://www.jamovi.org/jmv/), and the E-prime 3.0 software (Psychology Software Tools, Pittsburgh, PA, USA).

Differences between the groups of violent and non-violent patients and healthy controls in sex were analyzed by chi-square test, in age by Welch's ANOVA, and in education by Kruskal–Wallis ANOVA test (level of education was taken as an ordinal scale ranging from 1 to 4). Within-group effects in the ESST and BIS-11 were analyzed by paired t-tests, and between-group effects were analyzed by Welch's ANOVA (with results considered significant at level $p < 0.005$ after multiple comparisons correction) with Games-Howell post-hoc tests.

The analysis focused on violent psychotic patients firstly evaluated the differences between patients who were and were not able or willing to finish the behavioral task. Differences in BIS, PANSS and MOAS scores were examined by Mann–Whitney tests due to samples homogeneity violations in multiple variables. The results were considered significant at level $p < 0.005$ after to multiple comparisons correction. The relationships between behavioral data and self-reported measures were examined using non-parametric Spearman correlations.

Results

The sample of violent schizophrenia patients ($N = 117$, 60.7% men) aged from 18 to 67 years ($M = 35.77$, $SD = 9.87$). Twenty-five (21.6%) participants completed primary education, 37 (31.9%) completed lower secondary education, 39 (33.6%) completed higher secondary education, and 15 (12.9%) completed university. However, 66 individuals (56.41%) were not able or willing to complete the ESST. The differences between the behavioral and self-reported data of impulsivity were compared between violent patients who completed the task ($n = 51$) and two control groups. The demographic data of the three studied groups and between-group differences are presented in Table 1. The results showed no significant differences in age and sex distribution. There was a significant difference in the level of education between the groups. Violent psychotic patients achieved significantly lower levels of education that healthy controls; differences between the other groups were not significant.

Four patients from the violent group and one patient from the non-violent group were excluded from further analyses because of non-valid protocols (high percentage of *go* omissions). The within-group and between-group results of the ESST are summarized in Table 2. Regarding within-group effects: violent psychotic patients had lower accuracy and longer stop signal delay (SSD) in the angry condition than in the neutral condition, both patient groups had longer stop-signal reaction times (SSRT) in the angry condition than in the neutral condition, and healthy controls had higher *go* reaction times in the neutral condition than in the angry condition. Regarding the between-group effects: healthy controls had higher accuracy than both patient groups in the angry condition and than the non-violent patients in the neutral condition, and lower reaction times were found in non-violent patients in both angry and neutral conditions than in violent patients and healthy controls. Further, violent patients had higher SSRT than non-violent patients and

Table 1 Demographic data of studied groups and between-group differences

Variable		Violent patients ($N = 50$)	Non-violent patients ($N = 50$)	Healthy controls ($N = 50$)	Between group effects
Sex	men	$N = 27$ (54%)	$N = 30$ (60%)	$N = 24$ (48%)	Chi-square test
	women	$N = 23$ (46%)	$N = 20$ (40%)	$N = 26$ (52%)	$X^2(2, 149) = 1.449$, $p = 0.485$
Age (years)		$M = 38.2$	$M = 41.8$	$M = 38.1$	ANOVA (Welch's)
		$SD = 9.5$	$SD = 11.0$	$SD = 14.9$	$F(2, 95.264) = 1.766$, $p = 0.177$
Education	primary	$N = 10$(20.4%)	$N = 3$ (6%)	$N = 3$ (6%)	ANOVA (Kruskal–Wallis)
	lower secondary	$N = 14$ (28.6%)	$N = 14$ (28%)	$N = 6$ (12%)	**$X^2(2, 149) = 7.544$, $p = 0.023$, $eta^2 = 0.051$**
	higher secondary	$N = 16$ (32.7%)	$N = 24$ (48%)	$N = 29$ (58%)	SCH-V vs. SCH-N: $p = 0.317$
	university	$N = 9$ (18.4%)	$N = 9$ (18%)	$N = 12$ (24%)	**SCH-V vs. HC: $p = 0.023$**
					SCH-N vs. HC: $p = 0.281$

Table 2 Differences in ESST between violent and non-violent psychotic patients and healthy controls

Variable	Condition	1 SCH-V	2 SCH-N	3 HC	Within-group effects (t-test)	Between-group effects (ANOVA)
% *go* omissions	Angry	N = 46 **M = 0.467** SD = 0.262	N = 49 M = 0.514 SD = 0.233	N = 50 M = 0.315 SD = 0.246	**1: t(45) = 2.647, p = 0.011, d = 0.390** 2: t(48) = 1.356, p = 0.181, d = 0.194 3: t(49) = -1.023, p = 0.311, d = -0.145	**F(2, 93.842) = 9.013, *p* < 0.001** **1–3*, 2–3*****
	Neutral	N = 46 **M = 0.434** SD = 0.283	N = 49 M = 0.500 SD = 0.256	N = 50 M = 0.331 SD = 0.245		**F(2, 93.485) = 5.678, p = 0.005** **2–3****
GO RT	Angry	N = 45 M = 758.44 SD = 104.70	N = 49 M = 656.15 SD = 121.43	N = 50 **M = 727.90** SD = 88.20	1: t(43) = -0.160, p = 0.874, d = -0.024 2: t(48) = 1.405, p = 0.167, d = 0.201 **3: t(49) = -3.015, p = 0.004, d = -0.426**	**F(2, 91.452) = 9.933, *p* < 0.001** **1–2***, 2–3****
	Neutral	N = 44 M = 755.16 SD = 93.11	N = 49 M = 648.10 SD = 115.93	N = 50 **M = 746.77** SD = 94.31		**F(2, 92.456) = 14.315, *p* < 0.001** **1–2***, 2–3*****
% *stop* commissions	Angry	N = 46 M = 0.425 SD = 0.214	N = 49 M = 0.344 SD = 0.185	N = 50 M = 0.409 SD = 0.172	1: t(45) = -0.951, p = 0.346, d = -0.140 2: t(48) = -0.624, p = 0.536, d = -0.089 3: t(49) = 1.061, p = 0.294, d = 0.150	F(2, 92.839) = 2.403, p = 0.096
	Neutral	N = 46 M = 0.442 SD = 0.242	N = 49 M = 0.353 SD = 0.183	N = 50 M = 0.387 SD = 0.170		F(2, 91.468) = 2.002, p = 0.141
SSD	Angry	N = 46 **M = 355.70** SD = 203.67	N = 49 M = 449.24 SD = 190.03	N = 50 M = 417.81 SD = 176.20	**1: t(45) = -2.978, p = 0.005, d = -0.439** 2: t(48) = -1.481, p = 0.145, d = -0.212 3: t(45) = -0.593, p = 0.556, d = -0.084	F(2, 93.515) = 2.706, p = 0.072
	Neutral	N = 46 **M = 369.31** SD = 214.77	N = 49 M = 458.30 SD = 195.28	N = 50 M = 420.62 SD = 177.93		F(2, 93.142) = 2.208, p = 0.116
SSRT	Angry	N = 46 **M = 501.28** SD = 158.65	N = 49 **M = 384.78** SD = 121.97	N = 50 M = 382.63 SD = 111.18	**1: t(45) = 3.555, *p* < 0.001, d = 0.524** **2: t(48) = 2.290, p = 0.026, d = 0.327** 3: t(49) = -1.273, p = 0.209, d = -0.180	**F(2, 91.431) = 10.064, *p* < 0.001** **1–2***, 1–3*****
	Neutral	N = 46 **M = 478.44** SD = 158.99	N = 49 **M = 366.89** SD = 116.01	N = 50 M = 394.67 SD = 93.98		**F(2, 89.215) = 7.615, *p* < 0.001** **1–2***, 1–3****
BIS-11		N = 48 M = 71.25 SD = 9.59	N = 50 M = 59.16 SD = 5.68	N = 50 **M = 58.3** SD = 4.56	N/A	**F(2, 53.439) = 12.090, *p* < 0.001** **1–2***, 1–3*****

healthy controls in both angry and neutral conditions. Self-reported data showed significant differences between violent patients and both control groups. Results of both behavioral and self-reported impulsivity measures confirmed the group of violent patients as the most impulsive.

The next analyses were focused on correlations between the scores of self-reported measures and behavioral data in violent patients ($N = 46$; Table 3). Positive significant correlations were found between PANSS positive and SSRT in both angry ($r_s = 0.396$, $p = 0.008$) and neutral stimuli ($r_s = 0.427$, $p = 0.004$). Negative correlations were found between PANSS positive and SDD in both angry ($r_s = -0.308$, $p = 0.042$) and neutral stimuli ($r_s = -0.302$, $p = 0.046$). *Go* angry RT negatively correlated with PANSS disorganized ($r_s = -0.383$, $p = 0.010$), and *go* neutral RT correlated positively with PANSS excited/activation ($r_s = 0.315$, $p = 0.038$). No significant relationships were found between behavioral data and BIS-11, MOAS total score, or number of violent attacks.

Finally, we analyzed the differences between completers ($n = 51$) and non-completers ($n = 66$) of the emotional stop-signal task (ESST) in an attempt to explain what prevented the patients from completing the task. The results of self-reported measures (Table 4) showed significant differences between groups in the level of impulsivity. Non-completers scored significantly higher in the BIS-11 total score. More severe verbal aggression as measured by MOAS was found in non-completers, but the result did not hold after multiple comparison correction. Groups did not differ in schizophrenia symptoms. Based on these results, we suggest that high impulsivity, rather than psychotic symptoms, seems to be an underlying cause of failure in ESST.

Table 3 Results of Spearman's correlational analyses ($N = 46$)

	MOAS total score	Number of attacks	BIS-11	PANSS positive	PANSS negative	PANSS disorganized	PANSS excited/activation	PANSS anxious/depressed
Go angry omission	$r_s = -0.209$ $p = 0.164$	$r_s = 0.191$ $p = 0.203$	$r_s = 0.193$ $p = 0.204$	$r_s = 0.128$ $p = 0.407$	$r_s = -0.073$ $p = 0.637$	$r_s = -0.027$ $p = 0.861$	$r_s = -0.110$ $p = 0.476$	$r_s = 0.126$ $p = 0.416$
Go neutral omission	$r_s = -0.218$ $p = 0.145$	$r_s = 0.255$ $p = 0.087$	$r_s = 0.221$ $p = 0.144$	$r_s = 0.085$ $p = 0.583$	$r_s = -0.000$ $p = 0.998$	$r_s = -0.014$ $p = 0.928$	$r_s = -0.103$ $p = 0.506$	$r_s = 0.237$ $p = 0.121$
Go angry RT	$r_s = -0.185$ $p = 0.217$	$r_s = 0.232$ $p = 0.120$	$r_s = 0.063$ $p = 0.681$	$r_s = -0.026$ $p = 0.868$	$r_s = -0.231$ $p = 0.132$	**$r_s = -0.383$*** **$p = 0.010$**	$r_s = -0.264$ $p = 0.084$	$r_s = 0.233$ $p = 0.127$
Go neutral RT	$r_s = -0.051$ $p = 0.736$	$r_s = 0.082$ $p = 0.586$	$r_s = 0.067$ $p = 0.663$	$r_s = 0.091$ $p = 0.559$	$r_s = -0.003$ $p = 0.984$	$r_s = -0.102$ $p = 0.511$	$r_s = -0.150$ $p = 0.330$	**$r_s = 0.315$*** **$p = 0.038$**
Stop angry commissions	$r_s = 0.036$ $p = 0.812$	$r_s = -0.220$ $p = 0.141$	$r_s = -0.172$ $p = 0.260$	$r_s = 0.259$ $p = 0.090$	$r_s = 0.144$ $p = 0.353$	$r_s = 0.105$ $p = 0.499$	$r_s = 0.077$ $p = 0.621$	$r_s = -0.028$ $p = 0.858$
Stop neutral commissions	$r_s =$—0.157 $p = 0.297$	$r_s = -0.153$ $p = 0.310$	$r_s = -0.169$ $p = 0.266$	$r_s = 0.212$ $p = 0.167$	$r_s = 0.019$ $p = 0.901$	$r_s = 0.020$ $p = 0.899$	$r_s = 0.082$ $p = 0.597$	$r_s = 0.013$ $p = 0.933$
SSD Angry	$r_s = -0.113$ $p = 0.456$	$r_s = 0.210$ $p = 0.160$	$r_s = 0.096$ $p = 0.532$	**$r_s = -0.308$*** **$p = 0.042$**	$r_s = -0.191$ $p = 0.0.213$	$r_s = -0.115$ $p = 0.458$	$r_s = -0.104$ $p = 0.502$	$r_s = -0.045$ $p = 0.771$
SSD Neutral	$r_s = -0.135$ $p = 0.372$	$r_s = 0.185$ $p = 0.218$	$r_s = 0.132$ $p = 0.388$	**$r_s = -0.302$*** **$p = 0.046$**	$r_s = -0.176$ $p = 0.252$	$r_s = -0.094$ $p = 0.546$	$r_s = -0.085$ $p = 0.582$	$r_s = -0.024$ $p = 0.878$
SSRT Angry	$r_s = 0.059$ $p = 0.695$	$r_s = -0.112$ $p = 0.459$	$r_s = 0.023$ $p = 0.880$	**$r_s = 0.396$**** **$p = 0.008$**	$r_s = 0.095$ $p = 0.538$	$r_s = -0.020$ $p = 0.898$	$r_s = -0.041$ $p = 0.794$	$r_s = 0.240$ $p = 0.116$
SSRT Neutral	$r_s = 0.063$ $p = 0.678$	$r_s = -0.115$ $p = 0.445$	$r_s = -0.024$ $p = 0.878$	**$r_s = 0.427$**** **$p = 0.004$**	$r_s = 0.165$ $p = 0.283$	$r_s = 0.041$ $p = 0.793$	$r_s = -0.013$ $p = 0.931$	$r_s = 0.255$ $p = 0.095$

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 4 Differences between patients with and without ESST

Scale	With ESST		Without ESST		Mann–Whitney U test
	N	Mean (*SD*)	*N*	Mean (*SD*)	
PANSS					
Positive	49	20.61 (7.13)	66	20.56 (6.45)	$U = 1609.0$, $p = 0.966$, $r_{rb} = 0.005$
Negative	49	15.08 (6.28)	66	13.62 (6.97)	$U = 1437.0$, $p = 0.306$, $r_{rb} = 0.111$
Disorganized/Autistic preoccupation	49	15.88 (6.38)	66	15.20 (5.33)	$U = 1541.5$, $p = 0.671$, $r_{rb} = 0.047$
Excited/Activation	49	10.14 (5.30)	66	9.44 (4.15)	$U = 1532.0$, $p = 0.631$, $r_{rb} = 0.053$
Anxious-Depressed/Dysphoric	49	7.53 (3.32)	66	8.14 (3.77)	$U = 1495.0$, $p = 0.488$, $r_{rb} = 0.075$
MOAS total score	51	9.45 (3.28)	66	9.41 (3.41)	$U = 1666.5$, $p = 0.929$, $r_r = 0.010$
Verbal aggression	51	1.31 (0.86)	66	1.64 (0.92)	$U = 1310.5$, $p = 0.028$, $r_{rb} = 0.221$
Aggression against property	51	2.26 (2.39)	66	2.03 (2.23)	$U = 1622.0$, $p = 0.714$, $r_{rb} = 0.036$
Auto aggression	51	0.24 (1.18)	66	0.27 (1.37)	$U = 1672.5$, $p = 0.875$, $r_{rb} = 0.006$
Physical aggression	51	5.73 (3.42)	66	5.33 (3.67)	$U = 1591.5$, $p = 0.585$, $r_{rb} = 0.054$
BIS-11 total score	50	60.30 (9.93)	65	70.25 (15.32)	**$U = 882.5$, $p < 0.001$, $r_{rb} = 0.457$**

Discussion

The present study aimed to elucidate the response inhibition in emotional and neutral conditions in acutely violent psychotic patients and to compare it with non-violent psychotic patients and healthy controls. The longest SSRT, and thus the poorest response inhibition, was found in violent patients who differed from healthy controls and from non-violent patients. The result is consistent with previous literature on ESST since previous studies found no difference in SSRT between healthy people and non-violent schizophrenia patients in either emotional or angry conditions (Derntl & Habel, 2017) and found an association between aggression and higher SSRT in healthy volunteers (Pawliczek et al., 2013). No difference between non-violent psychotic patients and healthy controls was found. Thus, the current study suggests that violent behavior in

psychotic disorders is related to impaired response inhibition rather than to the disorder itself. On the other hand, we found a small significant positive association between SSRT and positive schizophrenia symptoms in the group of violent patients, suggesting that positive symptoms might fall into underlying factors of increased impulsivity in schizophrenia. Moreover, both patient groups showed impaired performance in *go* trials in comparison with healthy controls in both neutral and angry conditions, suggesting attention rather than inhibition deficit in schizophrenia in general. While impaired response inhibition has been suggested to be a reliable symptom in schizophrenia in general (Lipszyc & Schachar, 2010), it seems that it may instead constitute a marker for patients endangered with aggressive behavior. Thus, the evaluation of response inhibition deficits in patients with psychotic disorders is important and its role as a potential predictor of violent behavior in patients with schizophrenia spectrum disorders should be further studied.

Regarding the comparison between neutral and emotional conditions, both patient groups were found to have higher SSRT in the angry condition than in the neutral condition, and violent patients also had lower accuracy and higher SSD in the angry condition than in the neutral condition. The results contradict the results from a study by Derntl and Habel (2017) who found impaired inhibition in patients with schizophrenia only in the neutral condition. Other studies showed that neutral face processing is altered in schizophrenia patients and reported a tendency to overattribute anger to neutral stimuli in schizophrenia (Habel et al., 2010; Pinkham et al., 2011; Seiferth et al., 2009). Our results support the hypothesis that the perception of human faces in patients with schizophrenia is abnormal, but that this deficit is specifically related to the presence of violent behavior in patients. On the other hand, our results showed that the response inhibition in psychotic patients in general was worse in the angry condition than in the neutral condition. Acutely violent patients in our study seemed to be even more influenced by the angry faces since their accuracy in the *go* trials was lower in the angry condition than in the neutral condition. Moreover, we found that the higher the symptoms of disorganized thinking, the lower the *go* reaction times in the angry condition, and the lower the symptoms of excited/activation, the lower the *go* reaction times in the neutral condition, suggesting that mentioned psychosis symptoms might play a role in response facilitation in emotional situations, which might lead to more impulsive reactions. Similarly, we found higher *go* reaction times of healthy people in the neutral condition than in the angry condition, suggesting response facilitation in emotional situations even in healthy people. These results are consistent with studies that highlight the role of emotions in impulsivity and support the potentially important role in assessment of both emotion dysregulation and response inhibition in schizophrenia and psychotic patients.

However, we found that a complex behavioral impulsivity task such as the ESST might not be the most appropriate task for response inhibition assessment in highly impulsive and acutely aggressive patients with schizophrenia spectrum disorders since many patients might be unable or unwilling to complete the task. In our sample, about half of the violent patients were unwilling or unable to complete even the first part of the task. These respondents showed higher self-reported impulsivity and higher verbal aggression than the patients who completed the task. Based on the observations of the examiners, we identified two possible reasons – the task was too long or too boring for participants. This result suggests that high impulsivity seems to be an underlying cause of failure in ESST rather than psychotic symptoms and that simpler tasks should be considered when assessing response inhibition in acutely violent psychotic patients.

One limitation of our study is that only about half of the patients who acted violently completed the response inhibition behavioral task. Thus, the results might be influenced by the reduced sample variance. Moreover, only angry, and neutral stimuli were used in this study, so a generalization of the reactions of schizophrenia patients to other emotions is limited. We did not assess cognitive deficits in the psychotic patients that might play a role in response inhibition tasks (Derntl & Habel, 2017). Due to the small sample size, we could not analyze the influence of medication on response inhibition since the patients were under diverse types and combinations of treatment.

Despite the limitations, our study presents unique data on impulsivity and emotional facial processing in patients in acute stages of psychosis. It is in such acute stages that the patients are mostly endangered by aggressive behavior. Unlike in previous studies, we found worse response inhibition in both violent and non-violent patients in the emotional condition in comparison with the neutral condition. This means that higher impulsivity is related to the presence of emotions in patients with acute psychotic disorders and might be linked to emotion regulation deficits. This should be explored in future studies. The key finding of our study is that only the psychotic patients who acted aggressively showed impaired response inhibition (i.e., higher stopping impulsivity) in comparison with both healthy subjects and psychotic patients who were not aggressive, regardless of emotional or neutral condition. Thus, impaired response inhibition seems to be specific for violent psychotic patients rather than psychosis in general and may constitute a marker for the risk of violent behavior in psychotic patients. Future studies should explore the underlying mechanisms of impaired response inhibition in this group of patients and focus on the selection of more simple and effective methods

for successfully assessing response inhibition in acute psychotic patients.

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Data availability statement The data that support the findings of this study are available from the first author, [VJ], upon reasonable request.

Declarations

Conflicts of interest The authors declare no conflicts of interest.

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2.4 Indications from research on emotional impulsivity for the treatment of BPD

The findings of our studies on impulsivity in patients with BPD are consistent with the theoretical conceptualization of BPD as a disorder of emotion dysregulation. We found that patients with BPD exhibited increased impulsivity primarily in emotionally driven dimensions and during tasks involving emotional contexts. Our results also demonstrated impaired cognitive performance in emotional contexts, whereas no cognitive deficits were observed in emotionally neutral conditions. These findings support the hypothesis that cognitive functioning in patients with BPD deteriorates primarily during periods of heightened emotional arousal.

Furthermore, negative urgency—the tendency to act impulsively in response to negative emotions—emerged as the most clinically relevant dimension of impulsivity in BPD. It not only distinguished patients with BPD from healthy controls but also differentiated them from another highly impulsive clinical group, namely patients with ADHD. Importantly, negative urgency was associated with several indicators of clinical severity and healthcare utilization, including the number of suicide attempts and psychiatric hospitalizations.

Taken together, these findings suggest that effective treatment of BPD should primarily focus on strengthening patients' ability to regulate emotions in adaptive and effective ways, while also supporting cognitive functioning during emotionally challenging situations.

3 Neural correlates of borderline personality disorder

In the following chapter, we will discuss how the emotion dysregulation model aligns with current knowledge regarding the neural characteristics of patients with BPD.

With respect to neuroanatomical abnormalities, meta-analytic studies have consistently demonstrated reduced gray matter volume in the amygdala and hippocampus of patients with BPD compared with healthy controls (Davies, Hayward, Evans, & Mason, 2020a; O'Neill & Frodl, 2012; Schulze, Schmahl, & Niedtfeld, 2016; Visintin et al., 2016). The authors of these meta-analyses have noted that reductions in amygdalar and hippocampal volume are not specific to BPD but appear to be characteristic of individuals with a history of trauma exposure (Davies et al., 2020; O'Neill & Frodl, 2012). Given the high prevalence of traumatic experiences among individuals with BPD, the reduced volumes of the amygdala and hippocampus observed in this population may be attributable, at least in part, to trauma exposure rather than to BPD itself. Therefore, it is important to assess and account for lifetime trauma exposure in volumetric neuroimaging studies of BPD.

Regarding neurofunctional abnormalities, meta-analytic studies have consistently demonstrated increased amygdala activation in patients with BPD compared with healthy controls during exposure to emotional stimuli, particularly negatively valenced stimuli, as well as during tasks involving social cognition (O'Neill & Frodl, 2012; Schulze et al., 2016; Lars Schulze, Schulze, Renneberg, Schmahl, & Niedtfeld, 2019; Schurz et al., 2024). Amygdala hyperactivation represents the most widely accepted neurobiological explanation for emotional hyperreactivity in BPD and has therefore received substantial support across neuroimaging studies. According to Schulze et al. (2016), amygdala hyperactivity appears to be moderated by patients' medication status. According to this meta-analysis, increased amygdala activation was observed only in unmedicated patients with BPD, whereas medicated patients did not differ from healthy controls. These findings highlight the importance of considering medication status in functional neuroimaging studies investigating emotional processing in BPD.

Meta-analytic studies have further demonstrated reduced activation of the middle and inferior frontal gyri, as well as the dorsolateral prefrontal cortex (DLPFC), during tasks involving emotional processing and social cognition in patients with BPD (Schulze et al., 2016; Lars Schulze et al., 2019; Schurz et al., 2024). Lars Schulze et al. (2019) further demonstrated that hypoactivation of the right middle frontal gyrus appears to be a common feature of BPD, post-traumatic stress disorder (PTSD), and major depressive disorder, suggesting that it may reflect affective dysregulation more broadly. In contrast, hypoactivation of the dorsolateral prefrontal cortex (DLPFC) appeared to be more specific to BPD and may be associated with deficits in emotion regulation abilities. The combination of reduced activity in the inferior frontal gyri and DLPFC and increased amygdala activation is traditionally regarded as the neural correlate of disturbed emotional processing in BPD, reflecting impaired emotion regulation on the one hand and heightened emotional reactivity on the other.

Another area of functional disturbance observed in BPD is increased activity within the default mode network (DMN). The DMN is a distributed network of interconnected brain regions that includes the posterior cingulate cortex, precuneus, medial prefrontal cortex, and inferior parietal lobules (Davey, Pujol, & Harrison, 2016; Menon, 2023). DMN is activated during internally focused cognitive processes, self-reflection, autobiographical memory and internal reflection of our experiences and social interactions (Menon & Uddin, 2010). Hyperactivation of DMN (especially medial prefrontal cortex, precuneus, and cingulate cortex) in patients with BPD as compared to healthy controls has been robustly described by meta-analytic studies both in resting state and during emotional and social cognitive processing (Schulze et al., 2016; Lars Schulze et al., 2019; Schurz et al., 2024; Visintin et al., 2016). Based on the DMN functions, we can conclude that patients with BPD process emotional and social situations in more self-related way and they over-rely on self-related thought to understand mental states of others (Schulze et al., 2019; Schurz et al., 2024). This result also corresponds with our clinical experience in which patients with BPD often conflate their

emotional and mental states with others and they interpret social situations based on their self-referential thinking without checking the facts in the outside world.

In sum, the most recent meta-analytic evidence suggests that the principal neural correlates of BPD include reduced amygdalar and hippocampal volumes, which may be related to trauma exposure; increased amygdala activation and reduced activation of the inferior frontal gyri and dorsolateral prefrontal cortex during emotional and social processing, reflecting heightened emotional reactivity and impaired emotion regulation; and increased activity of the default mode network during both resting-state conditions and emotional or social tasks, potentially reflecting excessive self-referential processing. Overall, current knowledge regarding the neural characteristics of BPD provides strong support for the emotion dysregulation model and further underscores the importance of treatments aimed at helping patients regulate their emotions in adaptive and effective ways. In the following subchapters, two studies on the neural correlates of BPD conducted at our workplace are described.

3.1 Neural correlates of facial emotional processing in patients with BPD

As a part of our grant project supported by Ministry of Health of the Czech Republic no. NU20-04-00410 which explored behavioral and neural effectiveness of Dialectical behavior therapy (DBT) program in patients with BPD, we examined the neural differences using functional magnetic resonance imaging (fMRI) between the patients with BPD and healthy controls in two different tasks. In both parts of the study (Látalová et al., 2023; Radimecká et al., 2024), 30 patients with BPD (97% females, age: M = 24.2, SD = 5.2) and 30 matched healthy controls (97% females, age: M = 24.7, SD = 5.2) were included. In this commentary, I will focus on the results regarding the neural differences between the groups in the given tasks, rather than on the neural activation related to the task conditions as such which is further described in the publications (Annex 6 and Annex 7).

In the study of neural correlates of facial emotional processing (Radimecká et al., 2024), the "Faces task" (Paret et al., 2021) presented the participants with pictures of emotional human facial expressions (namely disgust, sadness, and fear) as compared with scrambled pictures as a control condition. Besides fMRI, we have also explored differences in heart rate variability (HRV) measured by electrocardiograph (ECG) during fMRI measurement. In previous studies (Koenig et al., 2017; Wainsztein et al., 2020; Weise et al., 2020), lower HRV was observed in patients with BPD and correlated with higher emotion dysregulation, and higher HRV is supposed to reflect the heart's ability to flexibly adapt to different emotional situations. The fMRI and HRV results were correlated with self-report results from scales measuring BPD symptoms.

The whole brain fMRI results showed no differences in brain activity between the groups in negative vs. control condition. The absence of between-group differences was found also in

the region-of-interest analysis focused on amygdala. This result was rather surprising because amygdala hyperactivity in patients with BPD is a stable finding in previous studies (see chapter 3), as well as because there were substantial differences in the self-reported symptomatology between the two groups. Moreover, amygdala activity was unrelated to symptom severity. We have discussed several possible reasons for these results. First, most of our patients were medicated. A single dose of citalopram was found to decrease amygdala activity during this task in patients with BPD (Paret et al., 2021), and a meta-analysis by Schulze et al. (2016) described that medicated and unmedicated patients with BPD show different neural activity. Thus, it is possible that psychiatric medication diminishes brain activity differences in response to emotional stimuli while the behavioral symptoms might not be affected by it. However, we could not test this hypothesis since most of our patients were under psychiatric medication.

Further, previous studies (Cullen et al., 2016; Mitchell, Dickens, & Picchioni, 2014; Wrege et al., 2021) found altered brain activity in patients with BPD mainly during watching fearful and neutral facial expressions. It is possible that mixing facial expressions of different emotions in our task might have diminished the between-group differences, and future studies should explore the brain correlates of separate emotions processing in patients with BPD. Moreover, because of altered processing of neutral faces in patients with BPD as compared to healthy controls, the neutral faces condition in previous studies might have also biased the results.

Moreover, we have found lower HRV in patients with BPD as compared to healthy controls, however it was unrelated either to task condition or to BPD symptoms. Although we did not observe task or symptom associations for lower HRV in the patients with BPD, it seems that lower HRV is connected with BPD in general. Future studies should explore not only neural, but also physiological correlates of disturbed emotional processing in BPD.

3.2 Neural correlates of social exclusion in patients with BPD

In the study of neural correlates of perceived social exclusion in patients with BPD (Látalová et al., 2023; Annex 7), we used the "Cyberball task" (Williams, Cheung, & Choi, 2000) which presents participants with a virtual ball tossing game where the participant exchanges a ball with two other virtual players. We explored three task conditions: exclusion (the players only exceptionally throw the ball to the participant), inclusion (the players throw the ball evenly to the participant and to each other), and overinclusion (the players throw the ball almost solely to the participant). The reasons for including the overinclusion condition were that some previous studies found that patients with BPD feel included only when they are actually overincluded (De Panfilis, Riva, Preti, Cabrino, & Marchesi, 2015; Weinbrecht, Niedeggen, Roepke, & Renneberg, 2018), and that previous studies did not explore the neural correlates of overinclusion in patients with BPD. The main behavioral dependent variable was the rating of how pleasant, or unpleasant the participants felt after each experimental condition type in

average (which was rated by the participants during the fMRI measurement directly after each condition). As in the previous study, associations between neural activity during the experimental conditions and self-reported BPD symptoms were also examined.

The behavioral results showed that, in both groups, the exclusion condition was rated as more unpleasant than the inclusion and overinclusion conditions, indicating that social exclusion is generally experienced as aversive, as expected. Importantly, patients with BPD rated all three experimental conditions as more unpleasant than healthy controls. This finding suggests that individuals with BPD experience greater emotional distress across a range of interpersonal situations, including those involving social inclusion, and further highlights the importance of targeting emotional responses in interpersonal contexts during treatment.

Regarding between-group neural differences, we observed greater activation of the left hippocampus in healthy controls than in patients with BPD in the exclusion-versus-inclusion contrast. Furthermore, in healthy controls, left hippocampal activity was negatively correlated with the severity of self-reported borderline and depressive symptoms. In patients with BPD, left hippocampal activity showed a significant negative correlation with the extent of self-reported childhood trauma. No significant neural differences were observed between the inclusion and overinclusion conditions in either group. Given the established role of the hippocampus in learning, memory encoding and consolidation, and emotional processing (Anand & Dhikav, 2012; Morgado-Bernal, 2011; Toyoda et al., 2011), it may be hypothesized that increased hippocampal activation in healthy individuals reflects adaptive attempts to regulate or attenuate the negative emotional impact of social rejection.

Another possible explanation for the reduced recruitment of the left hippocampus during social exclusion is the smaller hippocampal volume commonly observed in patients with BPD. Reduced hippocampal volume is one of the most consistent findings reported in meta-analytic studies of BPD (see Chapter 3), and hippocampal reductions have been repeatedly associated with a history of childhood maltreatment (Calem, Bromis, McGuire, Morgan, & Kempton, 2017; Paquola, Bennett, & Lagopoulos, 2016; Schmahl et al., 2009). Based on these findings, we included hippocampal volume as a covariate in an additional analysis. Consistent with previous studies, our results demonstrated that patients with BPD had a smaller left hippocampal volume than healthy controls. After controlling for hippocampal volume in the analysis of neural responses to social exclusion, the between-group difference in hippocampal activation was no longer significant. These findings suggest that the reduced recruitment of the left hippocampus during social exclusion observed in patients with BPD may be partly attributable to the reduced hippocampal volume characteristic of this population.

Overall, the findings of our study suggest that patients with BPD experience greater distress during social interactions than healthy controls. Compared with healthy participants, individuals with BPD reported higher levels of inner tension and more intense unpleasant emotions regardless of the degree of social inclusion they experienced. At the neural level, patients with BPD exhibited reduced recruitment of the left hippocampus in response to social

exclusion. This finding may be related to the high prevalence of childhood maltreatment in this population and the reduced hippocampal volume commonly observed in patients with BPD.

Annex 6

Radimecká, M., Látalová, A., Lamoš, M., Jáni, M., Bartys, P., Damborská, A., Theiner, P., **Linhartová, P.** (2024). Facial emotion processing in patients with borderline personality disorder as compared with healthy controls: An fMRI and ECG study. *Borderline Personality Disorder and Emotion Dysregulation*, 11: 4. doi: 10.1186/s40479-024-00245-4

Borderline Personality Disorder and Emotion Dysregulation

RESEARCH

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Facial emotion processing in patients with borderline personality disorder as compared with healthy controls: an fMRI and ECG study

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Abstract

Background Maladaptive behaviors and interpersonal difficulties in patients with borderline personality disorder (BPD) seem connected to biased facial emotion processing. This bias is often accompanied by heightened amygdala activity in patients with BPD as compared to healthy controls. However, functional magnetic resonance imaging (fMRI) studies exploring differences between patients and healthy controls in facial emotion processing have produced divergent results. The current study explored fMRI and heart rate variability (HRV) correlates of negative facial emotion processing in patients with BPD and healthy controls.

Methods The study included 30 patients with BPD (29 females; age: M = 24.22, SD = 5.22) and 30 healthy controls (29 females; M = 24.66, SD = 5.28). All participants underwent the "faces" task, an emotional face perception task, in an fMRI session simultaneously with ECG. In this task, participants are presented with emotional expressions of disgust, sadness, and fear (as a negative condition) and with the same pictures in a scrambled version (as a neutral condition).

Results We found no differences in brain activity between patients with BPD and healthy controls when processing negative facial expressions as compared to neutral condition. We observed activation in large-scale brain areas in both groups when presented with negative facial expressions as compared to neutral condition. Patients with BPD displayed lower HRV than healthy controls in both conditions. However, there were no significant associations between HRV and amygdala activity and BPD symptoms.

Conclusion The results of this study indicate no abnormal brain activity during emotional facial processing in patients with BPD. This result contrasts with previous studies and more studies are needed to clarify the relationship between facial emotion processing and brain activity in patients with BPD. Possible reasons for the absence of brain activity differences are discussed in the study. Consistent with previous findings, patients showed lower HRV than healthy controls. However, HRV was not associated with amygdala activity and BPD symptoms.

Keywords Borderline personality disorder, Facial emotion processing, Negative facial expressions, Faces task, fMRI, Heart rate variability

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Background

Emotional dysregulation, usually described as an inability to control and regulate one's affective state, is one of the core features in borderline personality disorder (BPD) [1]. It is linked with difficulties in the personal experience of emotion and with the perception of emotion in others [2, 3]. Given that facial expressions are fundamental emotional stimuli for everyday social functioning [4], biased processing of emotional faces in patients with BPD may lead to frequently observed maladaptive behaviors and interpersonal problems, including loneliness, conflictual relationships, and fear of abandonment.

Mitchell et al. [5] reviewed 25 studies ($N=1279$) exploring differences in facial emotion processing between patients with BPD and healthy controls (HC). They found conclusive evidence of a tendency in patients to interpret ambiguous and neutral expressions as negative expressions. However, the findings for negative and positive expressions have been divergent. Whereas some studies found impaired accuracy in recognizing a wide range of negative expressions [6], others found impairment only for specific expressions such as fear or disgust [7–9] or no impairment at all [10, 11]. Furthermore, no recognition difficulties were found in full-intensity happy expressions [12]. Patients were more accurate in recognizing happy faces than angry, sad, and neutral faces and displayed even greater accuracy than HC [6, 13].

Processing emotional expressions requires diverse psychological effort driven by multiple neural structures [14]. Fusar-Poli et al. [15] conducted a meta-analysis on 105 functional magnetic resonance imaging (fMRI) studies exploring the neural correlates of human facial expression processing in healthy respondents ($N=1600$). They found increased activation of various visual areas (fusiform gyrus, inferior and middle occipital gyri), limbic areas (amygdala and parahippocampal gyrus, posterior cingulate gyrus), temporal areas (middle and superior temporal gyrus), temporoparietal areas (parietal lobule, middle temporal gyrus, insula), prefrontal areas (medial frontal gyrus), and in the putamen and cerebellum. Although the specific interactions between these areas have not been clarified, it is hypothesized that the initial perceptual processing of faces occurs in the occipital and temporal lobes, which construct detailed representations from facial features. Subsequently, a set of brain areas, including the amygdala and orbitofrontal cortex, links the perceptual representation of the face to the meaning of the signaled emotion [15]. The amygdala is a crucial brain area associated with BPD symptoms, and studies often report its hyperactivity during emotional processing in patients [16]. Its activity may also be altered during the processing of facial expressions.

Recently, there has been an increase in fMRI studies exploring brain activity differences in patients with BPD. The review by Mitchell et al. [5] also described the differences in neural activation during facial processing between HC and patients with BPD. Heightened activity of the left and right amygdala in patients during the presentation of facial stimuli was found across studies. Specifically, patients with BPD exhibited increased amygdala activity in response to neutral stimuli and heightened amygdala activity in response to fear. A later study by Wrege et al. [17] presented images of faces with neutral and moderately fearful expressions (50%) or intensively (100%) fearful expressions to 39 patients with BPD and 25 HC. Besides higher amygdala activation, the results revealed higher activations when viewing neutral faces (neutral faces > fixation cross) in the right temporal pole, hippocampus, pallidum, and orbitofrontal cortex in the patients with BPD as compared with the HC. There were no group differences in whole-brain activation when viewing fearful facial expressions of both intensities (moderately fearful faces > fixation cross; intensively fearful faces > fixation cross). However, the region of interest (ROI) analysis (intensively fearful > neutral; moderately fearful > neutral faces) focused on the amygdala and hippocampus revealed higher bilateral amygdala and right hippocampus activity in response to moderately fearful expressions in patients with BPD as compared with HC. Lamers et al. [18] showed patients with BPD ($N=20$) and HC respondents only fearful faces stimuli. During this task, the patients with BPD showed hyperactivation of the frontostriatal, posterior cingulate cortex, and posterior parietal brain areas compared to HC (negative > neutral faces). ROI analysis also suggested higher activation in the emotion regulation network (amygdala, hippocampus, anterior cingulate cortex; ACC, insula, and dorsolateral prefrontal cortex) in the patients with BPD (negative > neutral faces) when compared to HC.

As for other negative emotions, Donegan et al. [19] presented patients with BPD ($N=15$) and HC with sad facial expressions. They found heightened left amygdala activity in response to sadness (sad faces > fixation point) in patients with BPD as compared with HC. Another study by Minzenberg et al. [20] used angry expressions in a sample of patients with BPD ($N=12$) and HC. In comparison to HC, the patients exhibited less activity in the bilateral amygdala, but more activity in the bilateral rostral ACC in response to angry expressions (anger > neutral faces). Baskin-Sommers et al. [21] also presented respondents ($N_{BPD}=13$) with angry expressions. In this study, patients with BPD demonstrated higher activity in response to anger in the left superior frontal gyrus (angry > neutral faces) relative to HC.

No unusual amygdala activity or typical patterns in brain activation were found regarding the processing of happy expressions in fMRI studies. Baskin-Sommers et al. [21] ($N_{BPD}=13$) found increased activity of the left inferior and decreased activity of the left superior frontal brain areas (happy > neutral faces); a more recent study by Lamers et al. [22] ($N_{BPD}=22$) did not replicate these findings. Besides the activity of temporal, limbic, and occipital areas in both groups, hyperactivation of the bilateral caudate was observed in the patients with BPD (happy > neutral faces).

With respect to the heterogeneous results of fMRI studies in this area, other methods might be useful to identify differences in facial processing between patients with BPD and healthy people. There has been increasing interest in heart rate variability (HRV) as a physiological marker of emotional stability and flexibility. HRV is the inconsistency of time intervals between individual heartbeats resulting from the balance between the sympathetic and parasympathetic branches of the autonomic nervous system [23]. Alteration of HRV emerges from the loss of balance between these branches and the constant need of the heart to adapt to changing circumstances. High HRV is associated with better adaptation to environmental stressors and emotional stimuli, whereas low HRV is associated with emotional dysregulation and worse ability to control mental and behavioral impulses [23, 24].

Fluctuations of HRV (as an index of cerebral autonomic regulation) are associated with functional changes between and within brain regions included in the central autonomic network (CAN; prefrontal cortex, anterior cingulate cortex, insula, amygdala, periaqueductal gray, pons, and medulla) [25–27]. Although imaging studies have pointed out that changes in the neural activity of the amygdala, claustrum, thalamus, and hypothalamus contribute to HRV [25, 28, 29], less is known about their relationship during emotion regulation and specifically facial emotion processing. Steinfurth et al. [30] explored the relationship between habitual resting state vmHRV and neural activity during explicit emotion regulation in healthy controls ($N=24$). The results showed an association between vmHRV and the activity of the prefrontal cortex (PFC) and amygdala during emotion regulation of unpleasant emotions. The group with high vmHRV displayed modulated activation of the right amygdala during the reappraisal strategy, and the group with low vmHRV displayed modulated activation of the right amygdala only when using the response modulation strategy. Similarly, respondents with high vmHRV displayed increased activation of the right PFC when regulating unpleasant emotion with reappraisal, whereas low vmHRV respondents displayed the same activation of PFC when using response modulation. Based on these results, the author suggested that different levels of vmHRV are associated with different patterns of brain activity during emotion regulation. A later study by Miller et al. [31] assessed neural activity and resting HRV while observing and imitating emotional faces in healthy respondents ($N=41$). They found negative correlation between resting HRV and activation in the mirror neuron system, insula, and amygdala during observation, but not the imitation of emotional faces. Thus, the results supported the idea, that resting HRV is linked to neural sensitivity to other's emotional cues, such as facial expressions.

Only a few studies have explored the alteration of HRV in patients with BPD. Koenig et al. [32] performed a meta-analysis on five studies ($N=200$) focused on vagally-mediated HRV (vmHRV) in patients with BPD and HC. Results revealed lower vmHRV in patients with BPD relative to HC in resting state. Later studies found a significant relation between reduced HRV and greater BPD symptom severity together with worsened psychosocial functioning and higher emotional dysregulation, negative affective state, and depressive symptomatology [33–35]. Therefore, differences associated with emotional dysregulation between patients with BPD and HC may be apparent in HRV.

To our knowledge, there has not yet been a study reporting HRV in patients with BPD during facial emotion processing. However, Maiß et al. [36] explored HRV during the approach-avoidance task (AAT) in 42 patients with BPD. In this task, respondents are presented with happy and angry expressions and must pull or push these pictures according to their reaction. The results indicated a relationship between low HRV and an attenuated approach to angry faces with an averted gaze, suggesting that patients have a tendency to avoid this facial expression.

To summarize, patients with BPD are consistently reported to show deficits in processing neutral or ambiguous facial expressions, which they tend to interpret as negative. This bias is usually accompanied by higher amygdala activity in fMRI studies. However, the findings of fMRI studies regarding facial processing of other emotional valence have been inconsistent. Some studies found heightened left amygdala activity in patients with BPD in response to sad expressions [19]; others found lowered bilateral amygdala activity and heightened activity of the bilateral rostral ACC or left superior frontal gyrus in response to angry expressions [11, 21]. In this study, we explored fMRI and HRV correlates of processing facial expressions with negative valence since patients often experience difficulties in negative social situations. For this purpose, we used the "faces" task [37]. All respondents were presented with negative facial expressions (disgust, sadness, and fear) and with scrambled pictures as a

control condition during fMRI with simultaneous electrocardiography (ECG) measurement. We did not use neutral expressions as a control condition because there is evidence of altered neural activation while viewing neutral faces in patients with BPD as compared to HC; this could diminish the activation differences associated with negative facial stimuli [17]. We used self-report questionnaires to assess fundamental symptoms of BPD (emotional dysregulation, rejection sensitivity, dissociation, and childhood trauma) that might affect emotional experiences during face processing in patients with BPD. We hypothesized that there are differences in neural activity between patients with BPD and HC while processing negative faces as compared to during a control condition. Based on previous studies, we specifically expected higher amygdala activity in the patients with BPD. We presumed that patients with BPD exhibit lower HRV than HC while viewing negative faces based on the previously found relationship of low HRV with emotional dysregulation. Lastly, in accordance with our previous suggestions, we expected higher amygdala activity to be associated with lower HRV during the processing of facial expressions in BPD patients.

Methods

Participants

This study was part of more extensive research exploring the neural mechanisms of dialectical behavioral therapy (DBT) in patients with BPD. The research was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Boards of the Faculty of Medicine, Masaryk University, and University Hospital Brno.

The current study was conducted before DBT treatment. We included 30 patients with BPD (29 females) and 30 matched HC (29 females). Patients with BPD were recruited from outpatient treatment at the Department of Psychiatry of the University Hospital Brno. Inclusion criteria were: 1) at least five out of the nine DSM-V criteria for BPD and 2) one or more suicide attempts and/or non-suicidal self-injury episodes in the past 6 months. Exclusion criteria were psychotic disorder, severe neurological disorder, or any contraindication to fMRI scanning. HC were recruited via social media advertisements. They were matched with patients in age (same age +/− 2 years), gender, and education (same level +/− one level). Educational levels were primary school, lower secondary, higher secondary, and university. Healthy controls had no current or lifetime psychiatric diagnosis.

Most patients (90%) also met the criteria for other psychiatric disorders, such as major depressive disorder (MDD) (50%), social anxiety disorder (33.3%), posttraumatic stress disorder (PTSD) (23.3%), substance use disorder (alcohol = 36.7%; drugs = 16.7%), obsessive-compulsive disorder (OCD) (13.3%), and panic disorder (13.3%). We also included medicated patients (83.3%). All participants were instructed not to take any sedative medication 24 hours before the fMRI session. They were allowed to take their other prescribed medication, consisting mainly of antidepressants and antipsychotics.

Since medication may alter neural activity [37, 38] we made a medication index to assess the possible effects of patient medication on neural activity. The medication index was made as an ordinary scale of medication according to Bartečků et al. [39]: 0 = no medication, 1 = one or more drugs at lower than the therapeutic dose, 2 = one drug at the therapeutic dose, 3 = more drugs with one at the therapeutic dose, 4 = more drugs at the therapeutic dose. Since major depressive disorder is one of the most common conditions that occur alongside BPD [40] and most prescribed medication in BPD patients includes antidepressants and antipsychotics [41, 42], we chose therapeutic doses of these two types of medication recommended for major depressive disorder. Therapeutic doses of antidepressants were specified according to the Antidepressant Treatment History Questionnaire (ATRQ; [43]). Therapeutic doses of antipsychotics were determined according to Wang et al. [44]. The medication index was then used as a covariate in statistical analyses.

Procedure

All of the participants were informed about the study before the assessments and gave their written informed consent. On the first day, participants attended a semi-structured interview with a trained psychiatrist and completed self-report questionnaires on BPD symptoms. The next day, they performed three tasks during fMRI, starting with the "faces" task. Then participants underwent the Neurofeedback task (assessing the emotion regulation ability) and the Cyberball task (assessing rejection sensitivity). The whole assessment took about two and a half hours. This study presents the fMRI data from the "faces" task and its relation to the self-report questionnaires. Results from the Cyberball task in the same sample were published in Látalová et al. [45] study.

Measurements

The BPD diagnosis was assessed by a trained clinician using the Structured Clinical Interview for DSM-V Personality Disorders [46].

Self-report questionnaires were used to assess the severity of BPD symptoms (Borderline Symptom List; BSL-23 [47]; Czech version: [48], emotional dysregulation (Difficulties in Emotion Regulation Scale Short Form; DERS-SF [49]; Czech version: [50], rejection sensitivity (Rejection Sensitivity RS-Adult questionnaire;

A-RSQ [51], and dissociation (Multiscale Dissociation Inventory; MDI [52]. We also assessed childhood trauma (Childhood Trauma Questionnaire CTQ [53]; Czech version: [54]). Since there is no validated Czech version of the A-RSQ and MDI questionnaires, we translated these questionnaires using the back-translation method.

Experimental task

We used the exact version of the "faces" task according to Paret et al. [37]. Participants viewed pictures of faces (12 actors and 12 actresses) with emotional expressions of disgust, sadness, and fear (negative condition; NgC) from the Warsaw Set of Emotional Facial Expression Pictures (http://www.emotional-face.org/), and the same pictures in a scrambled version (neutral condition; NC). In all, 72 emotional faces and 72 scrambled faces were used. The pictures were presented in 24 blocks (12 NgC and 12 NC), with the order pseudorandomized with maximally two identical conditions following each other. Every block consisted of a sequence of six faces, each presented for 3 seconds. Within each block, faces with different emotional expressions of different people occurred randomly. The inter-block interval included a fixation cross on a black background, lasting randomly between nine and 11 seconds. To maintain attention, we instructed respondents to press the left or right button according to the gender of the presented face (NgC) or the color of the frame around the picture (NC).

Functional and structural MRI acquisition and ECG

The acquisition was performed on the Siemens Prisma 3 T MR whole-body scanner with 64-channel head-neck coil. A high-resolution structural T1 image was scanned for each participant. This makes it possible to localize the active brain areas more accurately than using functional images only. Parameters of the MPRAGE sequence were 240 sagittal slices, repetition time (TR) = 2300 ms, echo time (TE) = 2.34 ms, field of view (FOV) = 256 mm, flip angle = 8°, slice thickness = 1 mm). Functional blood-oxygen-level dependent (BOLD) MR data were acquired in a single scanning session with a T2*-weighted multiecho multiband echo-planar imaging (ME MB EPI) sequence of 1250 scans (60 slices, TR = 1000 ms, TE = 14, 34.63 and 55.26 ms, FOV = 200 mm, flip angle = 50°, slice thickness = 2.5 mm, MB factor = 5). TE values were chosen according to recommendations for ME EPI [55], where the second echo was very close to the typical value of single echo acquisition. Simultaneously with the fMRI data, ECG and respiration were measured by Brain Products BrainAmp ExG MR system with 5 kHz sampling frequency. Both signals were corrected for MR gradient artifacts [56] in Brain Vision Analyzer 2 and then used for RETROICOR correction of fMRI data. Processed ECG signal was also used for HRV calculation.

Data analysis

Self-reported data

Self-reported data were analyzed in IBM SPSS Statistic (Version 27) [57]. Independent t-tests were performed to explore group differences in age and in self-report questionnaires. The Mann-Whitney U test was used to assess differences in the level of education between patients and HC.

fMRI data pre-processing

All scans were realigned first. The process was applied to middle echo scans when each middle echo scan was aligned to the first middle echo scan. Estimated translations and rotations were used in the realignment procedure of other echoes. RETROICOR technique [58] suppressed any physiological noise originated in ECG and respiration in all scans. Information from all three echoes was used to create a composite scan using the contrast-to-noise weighted average. In each voxel, temporal SNR (tSNR) values were computed for each echo. The resulting voxel value was given by the weighted average of the three original tSNR-weighted values and echoes [59, 60]. Composite functional scans were then coregistered to high resolution structural T1-weighted images and all data were normalized to the Montreal Neurological Institute (MNI) template. As a last step, the spatial smoothing of functional data was calculated by Gaussian filter with full-width at half-maximum (FWHM) of 5 mm.

The data quality was checked for the presence of spatial abnormalities in Mask Explorer [61] and for the presence of excessive movement in the movement_info tool (https://www.nitrc.org/projects/movement_info). The movement in the data was controlled by a frame-wise displacement (FD) measure [62]. Data from all participants were eligible using the thresholds of 20% of scans exceeding FD = 0.5 mm and 1% of scans exceeding FD = 1.5 mm [59].

fMRI data analysis

The data were processed with SPM12 toolbox (http://www.fil.ion.ucl.ac.uk/spm) running under MATLAB R2021a [63]. General linear modelling (GLM) was used to analyze the pre-processed data.

At first, the difference between NgC and NC condition and the comparison between BPD and HC group were examined. GLM was performed on the subject level, where the design matrix contained three time courses of visual stimuli timings convolved with canonical hemodynamic function and six confound regressors for movement (translations and rotations from realignment

pre-processing procedure). The task was modelled as a block design, where three time courses represent the NgC blocks, the NC blocks, and the inter-block interval. First-level contrasts correspond to NgC and NC and their difference.

In the next step, group level GLM analysis was performed. We used a two-sample t-test to find the differences between patients with BPD and HC. Group results were evaluated at the cluster level inference with an initial cut-off of $p < .001$ and cluster size larger than 20 and $p < .05$ with FWE correction on the cluster level. For the evaluation of the NgC and NC difference across all measured subjects one-sample t-test was used. The Xjview 10.0 toolbox was used to display results [64].

To assess the effect in the region of interest (ROI) only, the pipeline was the same as for the whole brain analysis. The amygdala region was selected based on masks created from automated anatomical labeling (AAL) atlas. The ROI representative was extracted as a mean of voxels assigned to the ROI. The extraction was performed on contrast estimates (NgC – NC). The medication effect was first shown using the medication index as a covariate in the group level GLM analyses. Then, statistical comparison between contrast estimates with and without medication was computed by paired t-test. For the analysis of amygdala habituation, the task regressors in the subject level GLM model were modulated by linear function, which characterizes the linear change of the effect over time. In the SPM model, the specifications of the first order time modulation were selected for task regressors. Time modulation of regressors allows for the characterization of nonstationary responses, e.g., habituation. We modeled linear effect/linear change of heights in regressors over time. This approach was used, for example, in Peters et al. [65]. The advantage lies in using all scans in one model, which provides a better signal-to-noise input into the model than comparing the average BOLD signal from 18 seconds of first and last blocks. Random order of the blocks (with max 2 repetitions consequently) also didn't allow to split each subject data into two parts of the same length.

Correlation analyses were conducted to examine associations between amygdala activity, specifically, HRV, and BPD symptoms.

Heart rate variability

ECG data were preprocessed in the BrainVision Analyzer 2 [66]. MR gradient artifacts were suppressed by a subtraction approach [56]. The data were resampled to a 250 Hz sampling rate and filtered with the Butterworth zero phase low pass filter with a cut-off at 40 Hz. Then, R waves were detected by a template matching procedure and manually checked with a visual inspection.

The standard deviation of heart rate values was computed in the NgC blocks as the heart rate variability (HRV) parameter. The comparison between the patients with BPD and HC groups were calculated using a Wilcoxon rank sum test in MATLAB R2021a. Correlation analyses were conducted to examine associations between HRV and BPD symptoms.

Results

The results of the independent t-test showed no significant differences between BPD and HC groups in age. Significant between-group differences were found in BSL-23, A-RSQ, DERS-SF, MDI, and CTQ scores. In all questionnaires, patients with BPD had significantly higher scores than HC. A Mann-Whitney U test suggested a significant difference in education. Details are presented in Table 1. Since there was a significant difference in educational level between groups, the possible effect of education on self-report questionnaires was explored by ANCOVA (using education as a covariate). Results showed no effect of education on differences between the groups in any of the self-report questionnaires.

fMRI results

The between-group comparison did not show any significant whole-brain differences between patients with BPD and HC in the NgC contrasted to the NC. Further, we performed a region of interest (ROI) analysis focused on the differences between groups specifically in the amygdala. The ROI analysis revealed no significant differences between patients and controls in amygdala activation.

As we identified no differences in fMRI between the groups, we compared the task conditions on the whole sample. The cluster-level whole-brain analysis identified eight large clusters in the NgC contrasted to NC condition (contrast NgC minus NC). Clusters had activation peaks in the cerebellum posterior lobe, hippocampus, thalamus, amygdala, medial frontal gyrus, putamen, superior and frontal gyrus, precuneus, and cingulate gyrus (Fig. 1). A detailed description of clusters is provided in Table 2.

To assess the effect of educational level, statistical comparison between contrast estimates (NgC minus NC) with and without educational level as a covariate was computed by paired t-test. Results showed no significant differences.

Additional analyses

Medication effect

The results showed no significant differences between contrast estimates (NgC minus NC) with and without medication (Fig. 2).

Table 1 Demographic and clinical characteristics of the study sample

	BPD patients		HC		BPD vs HC independent t-test		
	N = 30		*N* = 30				
	M	SD	M	SD	T (df)	*p*-value	D
Age	24.2	5.2	24.7	5.2	- 0.3 (58)	0.74	5.2
BSL-23	51.7	14.0	5.7	5.5	16.7 (37.9)	< .001	10.6
A-RSQ	15.3	4.8	6.5	2.8	8.5 (58)	<. 001	4.0
DERS-SF	61.5	7.3	31.0	6.6	16.9 (58)	<. 001	6.9
MDI	72.2	18.0	38.4	7.4	9.5 (38.6)	<. 001	13.7
CTQ	58.1	13.4	32.3	5.8	9.5 (37.8)	<. 001	10.2
Education	N		N		Mann-Whitney U test		
					U	*p*-value	r
Primary	6		4		310	.025	.031
Lower secondary	4		0				
Higher secondary	16		15				
University	4		11				

BPD borderline personality disorder, *HC* healthy control, *M* mean, *SD* standard deviation, *BSL-23* Borderline Symptom List, *A-RSQ* Rejection Sensitivity Questionnaire, *DERS-SF* Difficulties in Emotion Regulation Scale Short Form, *MDI* Multiscale Dissociation Inventory, *CTQ* Childhood Trauma Questionnaire

Amygdala habituation

Some authors have suggested that it might not be that the average amygdala activity is impaired in patients with BPD during emotional stimuli, but rather that patients with BPD show lower habituation on emotional stimuli as compared with HC [67, 68]. Since we did not find differences in amygdala activity between the groups, we also explored differences in amygdala habituation. The group comparison results did not show differences in amygdala habituation between the patients with BPD and HC ($t = 4.55$; $p_{FWE} = .47$).

Heart rate variability results

The results showed significantly lower HRV in patients with BPD than in HC ($p = .004$; $r = .35$) in NgC condition, as illustrated in Fig. 3. HRV was significantly lower in patients also in NC condition ($p = .003$, $r = .35$). No differences were found within-groups in NgC versus NC condition (BPD group: $p = .70$; $r = .007$; HC group: $p = .52$; $r = .03$).

Correlation analyses

Amygdala activity and HRV

No significant correlations were found between the left amygdala and HRV ($r = .12$, $p = .53$) and the right amygdala and HRV ($r = .11$, $p = .56$) in BPD patients. No significant correlations were found between the left amygdala and HRV ($r = -.01$, $p = .95$) and the right amygdala and HRV ($r = .09$, $p = .65$) in healthy controls.

Amygdala activity and self-report questionnaires

Since no differences were found in amygdala activity between groups, correlations were performed on the whole sample. No significant correlations were found between the left amygdala activity and BSL-23 ($r = -.08$; $p = .54$), A-RSQ ($r = -.07$; $p = .58$), MDI ($r = -.07$; $p = .55$), DERS-SF ($r = -.03$; $p = .79$), or CTQ ($r = -.06$; $p = .61$) scores. No significant correlations were found between the right amygdala activity and BSL-23 ($r = -.20$; $p = .11$), A-RSQ ($r = -.02$; $p = .87$), MDI ($r = -.13$; $p = .31$), or DERS-SF ($r = -.13$; $p = .32$) scores.

Heart rate variability and self-report questionnaires

No significant correlations were found between HRV and BSL-23 ($r = -.15$; $p = .43$), A-RSQ ($r = .15$; $p = .43$), MDI ($r = -.19$; $p = .31$), DERS-SF ($r = .33$; $p = .09$), and CTQ ($r = .04$; $p = .81$) scores in patients with BPD. As well in HC, no significant correlations were found between HRV and BSL-23 ($r = -.00$; $p = .99$), A-RSQ ($r = .08$; $p = .67$), MDI ($r = .24$; $p = .22$), DERS-SF ($r = -.04$; $p = .83$), or CTQ ($r = .17$; $p = .38$).

Discussion

The current study explored fMRI and HRV correlates of negative emotional facial processing in patients with BPD and HC. We found large scale activation across the brain in the whole sample while processing negative facial expressions as compared to the control condition (scrambled pictures). Contrary to our hypotheses, we found no significant differences between patients with BPD and HC in neural

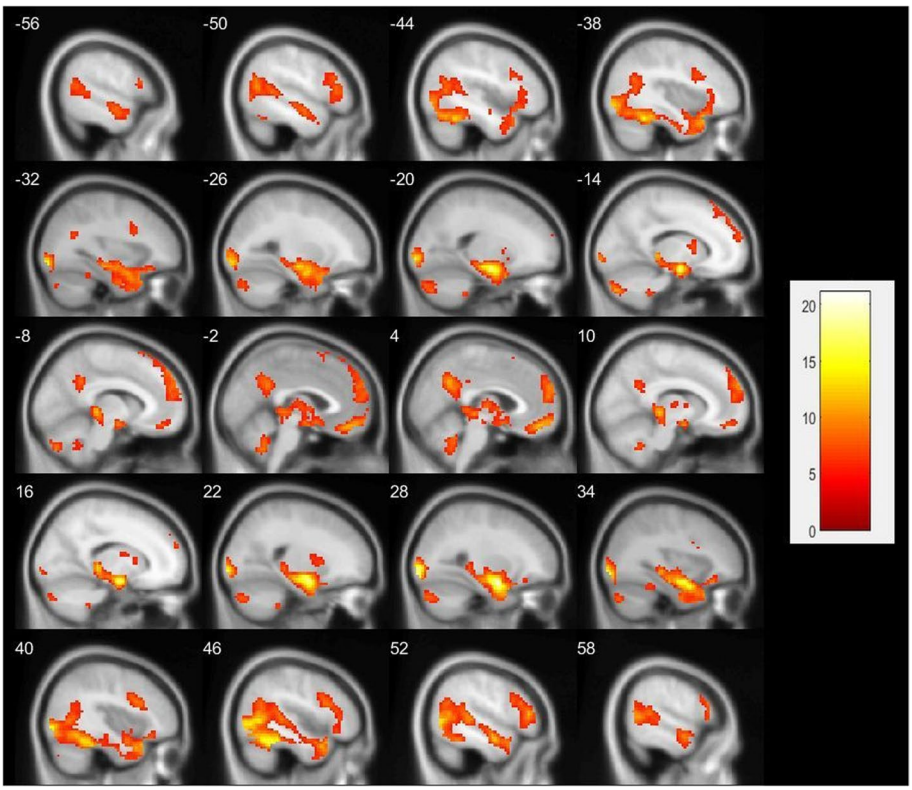

Fig. 1 Activation map showing areas with higher activation during negative facial processing in all subjects (patients with BPD and HC together). Shown areas represent higher activity at threshold p(FWE) < .05 (contrast NgC minus NC)

activity nor higher amygdala activity specifically in patients with BPD as compared with HC when processing negative facial expressions as compared to the control condition. Moreover, amygdala activity was unrelated to BPD symptom severity. The results suggest no abnormal BOLD activity during negative emotional facial processing in patients with BPD. Further, patients with BPD displayed lower HRV as compared with HC, regardless of condition type. However, there was no significant association between HRV and BPD symptoms, rejection to sensitivity, dissociation, emotional dysregulation, and childhood trauma as measured by self-report questionnaires both in patients with BPD and HC. These findings indicate that low HRV may be

Table 2 fMRI whole-brain results associated with negative facial expression processing as compared to scrambled pictures (contrast NgC minus NC) in all respondents. Results significant on the cluster level with FWE correction $p < .05$

Anatomic label	Side L/R	Peak MNI coordinate			Peak intensity (t)	Cluster size	$P_{FWE-cor}$
		X	Y	Z			
Cerebellum posterior lobe	L	−3	−58	−44	8.92	168	<.001
Cerebellum posterior lobe	L	−15	−82	−41	10.57	158	<.001
Hippocampus, thalamus, amygdala	R	27	−1	−20	21.07	6156	<.001
Cerebellum posterior lobe	R	24	−82	−35	8.30	119	<.001
Medial frontal gyrus	Medial	0	47	−17	12.39	234	<.001
Putamen	L	−12	11	4	7.44	44	<.001
Superior frontal gyrus, medial frontal gyrus	R	9	59	28	9.67	552	<.001
Precuneus, cingulate gyrus	R	3	−58	34	10.71	268	<.001

The anatomic label of the peak voxel is shown. *BPD* borderline personality disorder, *HC* healthy control, *L* left, *R* right, *MNI* Montreal Neurological Institute (x, y and z coordinates are provided in mm), *Cluster size* the number of voxels, *NgC* negative condition (negative emotional faces). *NC* neutral condition (scrambled pictures)

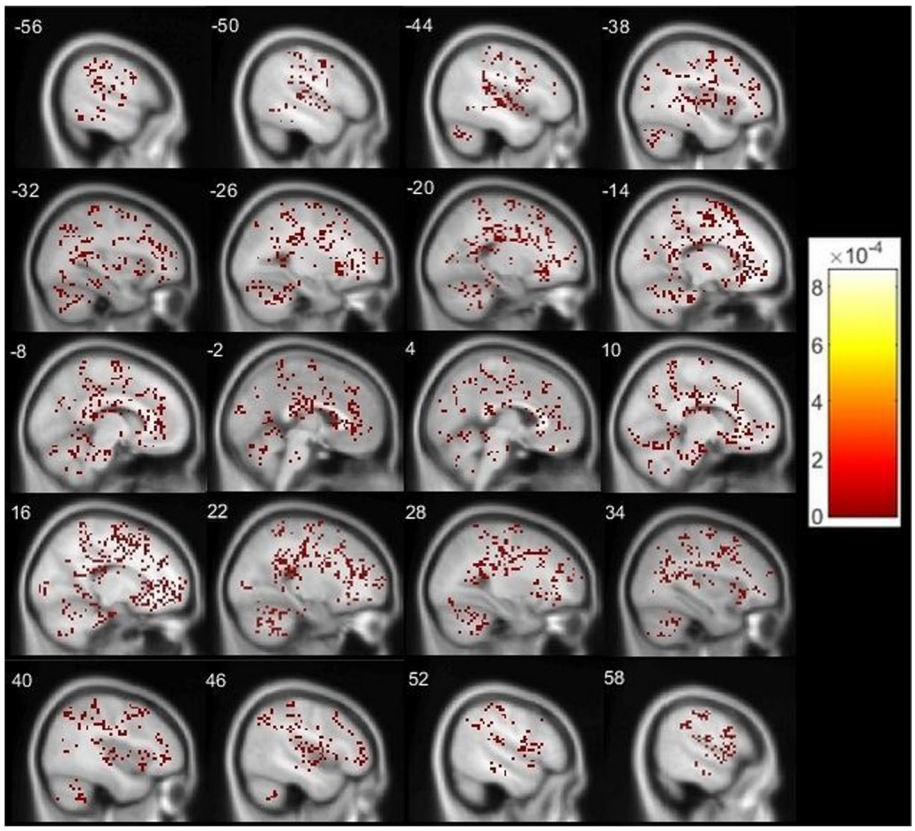

Fig. 2 Results of the comparison of contrast estimates (NgC minus NC) with and without medication

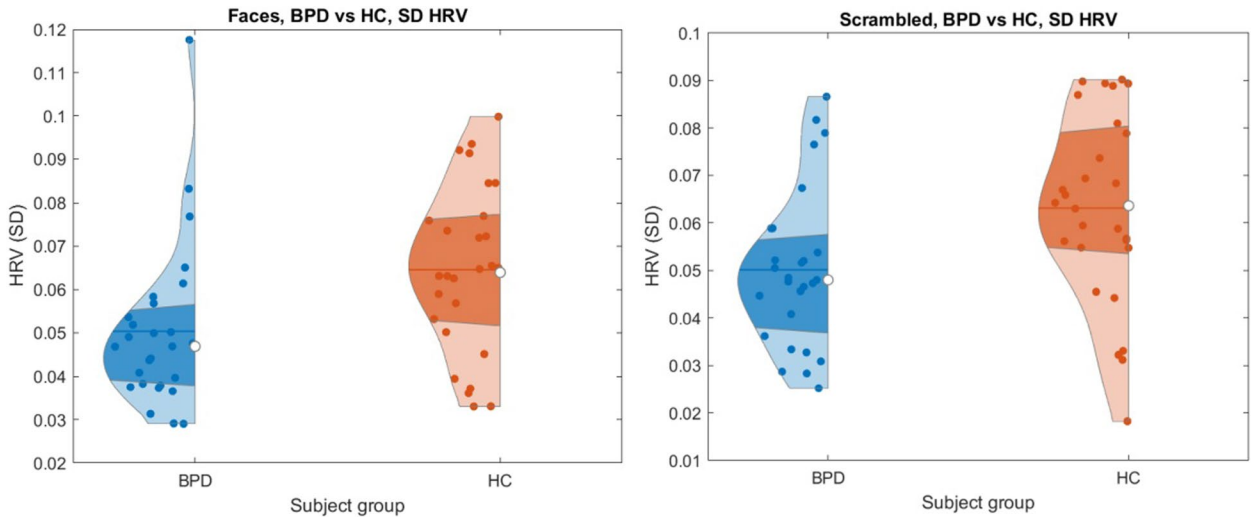

Fig. 3 Differences between patients with BPD and HC during the NgC ($p = .004$; $r = .35$) and NC ($p = .003$; $r = .35$) condition

associated with BPD, but it was unrelated to experimental condition and symptoms assessed in this study.

In the whole sample, we found heightened activity in the cerebellum posterior lobe, hippocampus, thalamus, amygdala, medial frontal gyrus, putamen, superior frontal gyrus, precuneus, and cingulate gyrus. Activity in the superior frontal gyrus, precuneus, hippocampus, amygdala, putamen, and medial frontal gyrus was also found

in previous studies exploring brain activity during facial processing in HC and patients with BPD [12, 15, 21, 22]. Thus, the "faces" task seems a valid method for eliciting the activity of areas connected to facial emotion processing. However, differences between patients with BPD and HC were not detected by the "faces" task in this study, although the differences in self-reported BPD symptoms between the groups were very high.

Several factors may explain the discrepancy between our findings and previous findings regarding brain activity and mainly amygdala activity during facial processing in patients with BPD. Previous studies found amygdala hyperactivity in patients while viewing neutral and fearful expressions [5, 12, 17]. In the current study, we presented respondents with mixed expressions of fear, disgust, and sadness. Wrege et al. [17] pointed out that the neural substrates of emotion processing seem to be task-dependent and affected by the type of comparison. Thus, it is possible that combining negative expressions of different emotions might have diminished amygdala hyperactivity or brain differences between groups in general. Moreover, there seem to be fMRI correlates during facial expression experiencing other than the amygdala. For example, studies found heightened activity of the superior frontal gyrus [17, 18, 21], medial frontal gyrus [12, 15], hippocampus [18, 69], and precuneus [12, 17, 18]. Other studies did not find heightened amygdala activity [18, 20]. It is possible that amygdala activity is heightened primarily in processing neutral or fearful expressions; therefore, various emotional valences should be explored separately. Moreover, altered brain activity to neutral faces in BPD is a stable finding [5, 17]; using neutral faces as a control condition for comparing to negative faces might be therefore biased. It follows that the relationship between higher amygdala activity and processing negative facial expressions is not straightforward.

According to some studies [67, 68], differences between patients with BPD and HC in emotion processing are not connected to amygdala hyperactivity but rather to slower amygdala habituation in patients. Following this hypothesis, we also analyzed differences in amygdala habituation to investigate the possibility of this effect. However, we did not find significant differences in habituation, thus we can rule out this process in our study and support previous ideas.

Studies by Frick et al. [70] and Mier et al. [71] that identified amygdala hyperactivity in patients with BPD during neutral and negative expressions used tasks in which the respondents were instructed to identify the presented facial emotion. Following the procedure from Paret et al. [37], respondents in our task were instructed to identify gender on the facial pictures to maintain their attention while viewing the faces. It is possible that neural correlates identified in previous studies might have reflected the emotion recognition process, not only the emotional experience while viewing faces. However, further research is needed to explore how ways of maintaining attention may affect these tasks. We may speculate that passive viewing of emotional expression is insufficient to detect abnormalities in brain processing of emotional faces in patients with BPD, even though Donegan et al. [19] found heightened amygdala activity even in this type of task. It is also possible that identifying gender on the face pictures might have diminished the power to detect differences between the groups.

Another possible influence in our study is patient medication. According to Schulze, Schmahl and Niedtfeld [72], medication considerably influences neural activations of the left amygdala and hippocampus. In their study, medication-free patients displayed hyperresponsivity to negative stimuli compared to HC. However, no hyperresponsivity was found in patients with BPD currently taking various psychotropic medication. This suggestion was supported by a later study by Paret et al. [37], in which a single dose of citalopram reduced bilateral amygdala activity while viewing negative affective expressions in the same task that was used in the current study. Since we included mostly medicated patients (83.3%) in our study, we analyzed the possible effect of medication. However, we did not find significant differences in neural activity with and without medication. Thus, we can rule out the effect of the medication on neural activity in this study. Nevertheless, we cannot rule out the effect of the medication completely since we had one group with various kinds of medications and the second group without any medication.

This study's second focus was examining HRV differences during facial emotion processing. Compared to HC, patients exhibited lower HRV when viewing both negative expressions and scrambled pictures. This finding suggests that patients generally have a lower HRV compared to HC. However, we did not find a significant relationship between HRV and amygdala activity in the patient group. The absence of this relationship might be explained by no differences in amygdala activity between patients and healthy controls. Also, there was no relationship between HRV and BPD symptom severity, rejection sensitivity, dissociation, emotional dysregulation, or childhood trauma. This result contrasts with previous studies [33–35, 73, 74]. A possible explanation may lie in methodological differences. The studies that found a positive relationship between HRV and BPD measured HRV outside the fMRI, whereas we measured HRV in fMRI. Although we did not clarify the association between lower HRV and BPD symptoms, low HRV seems to be connected to a worsened ability to react to emotional

stimuli [33–35] and it might underlie disturbed emotion processing in BPD. A possible explanation for why group differences were found in HRV and not in fMRI may lie in the RETROICOR preprocessing technique. This routinely used technique suppresses the variability associated with physiological noise in the context of fMRI data, including the heart pulsation. On the basis of the timing of R-waves in the ECG, basic functions are regressed from fMRI, which suppresses undesired physiological artifacts and enhances the signal-to-noise ratio [58, 75]. In our case, a partial suppression of the desired effect might occur. In general, it seems appropriate to assess emotional dysregulation by various markers, including both fMRI and psychophysiological functions. According to our expectations, BPD patients have lower HRV in general. Although we still do not know what processes underlie lower HRV in patients, it was not task dependent in our study.

Several limitations of this study should be discussed. As mentioned, we used the "faces" task with a combination of negative expressions instead of focusing on one specific emotion. Presenting more than one emotion and quickly changing among several expressions may affect neural activity and diminish potential differences. Although this may be understood as a limitation, this "faces" task design is diverse and complex, thus resembling social interactions in everyday life.

Because of our sample composition, we cannot generalize results to men. We also did not exclude patients with BPD with comorbid disorders. Therefore, we cannot reject the possibility that the absence of diversity in neural activity and lower HRV are associated with patient comorbidities. However, comorbid disorders are natural in patients with BPD. Moreover, most of our BPD patients were medicated, thus we cannot rule out the medication influence completely, and further studies could include a direct comparison of medicated and unmedicated patients.

Previous studies and reviews [5, 12, 17] provided evidence about abnormal amygdala activity of patients with BPD during facial emotion processing. However, we did not find any differences in brain activity. The relationship between BPD symptoms and the amygdala seems more complex, and more research is needed. Future research should explore neural activity connected to specific emotional valence rather than multiple emotions. It is also necessary to clarify the role of medication in changing neural activity and comorbidity in HRV abnormality. Although low HRV seems connected to emotional instability and worsened ability to react to emotional stimuli [33–35], more studies are needed to better understand its relationship.

Conclusions

To our knowledge, this is the first study exploring brain activity together with heart rate variability and their relationship during facial emotion processing in BPD patients. We did not find any differences between patients and healthy controls in brain activity, neither in amygdala, specifically. Further, there were no difference in amygdala habituation during the task between the groups. Although heightened amygdala activity is a frequently reported result, it seems that its connection to facial emotion processing is not straightforward, and future studies should explore its activity during specific emotional valence rather than multiple emotions. The results showed lower HRV in patients with BPD than in healthy controls, but HRV was not associated with BPD symptoms. Therefore, low HRV seems to be connected to the emotion dysregulation disorder, however its relationship to specific symptoms or functions needs to be clarified.

Abbreviations

AAT	Approach Avoidance Task
ACC	Anterior cingulate cortex
A-RSQ	Rejection Sensitivity Questionnaire
BOLD	Blood-oxygen-level dependent
BPD	Borderline personality disorder
BSL-23	Borderline Symptom List
CAN	Central autonomic network
CTQ	Childhood Trauma Questionnaire
DERS-SF	Difficulties in Emotion Regulation Scale Short Form
DMN	Default mode network
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
FD	Framewise displacement
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
FOV	Field-of-view
FWE	Family-wise error
FWHM	Full width at half maximum
GLM	General linear modelling
HC	Healthy control
HRV	Heart rate variability
L	Left
M	Mean
MDD	Major depressive disorder
MDI	Multiscale Dissociation Inventory
ME MB EPI	Multiecho multiband echo-planar imaging
MNI	Montreal Neurological Institute
N	Number of participants
NC	Neutral condition
NgC	Negative condition
OCD	Obsessive-compulsive disorder
PFC	Prefrontal cortex
PTSD	Posttraumatic stress disorder
R	Right
ROI	Region of interest
SCID-5-PD	Structured Clinical Interview for DSM-5 Personality Disorders
SD	Standard deviation
TE	Time to echo
TR	Repetition time
vmHRV	Vagally mediated heart rate variability

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Authors' contributions
MR, AL, MJ, and PB recruited the participants and assisted at the fMRI sessions. AD, PT, and MR conducted the clinical interviews. ML programmed the fMRI task and analyzed the fMRI and ECG data. MR and AL analyzed the self-report data. PL aided in interpreting the results and supervised the whole project. MR wrote the manuscript with the help of PL, AL, AD, and ML. All of the authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The research was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Board of the Faculty of Medicine, Masaryk University, and by the Ethics Board of the University Hospital Brno. All participants were informed about the study before assessments and provided their written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Publisher's Note

Annex 7

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Borderline Personality Disorder and Emotion Dysregulation

RESEARCH

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Neural correlates of social exclusion and overinclusion in patients with borderline personality disorder: an fMRI study

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Abstract

Background Interpersonal difficulties of patients with borderline personality disorder (BPD) are closely related to rejection sensitivity. The aim of the present study was to gain further insight into the experience and cerebral processing of social interactions in patients with BPD by using fMRI during experimentally induced experiences of social exclusion, inclusion, and overinclusion.

Methods The study involved 30 participants diagnosed with BPD (29 female and 1 male; age: M = 24.22, SD = 5.22) and 30 healthy controls (29 female and 1 male; age: M = 24.66, SD = 5.28) with no current or lifetime psychiatric diagnoses. In the fMRI session, all participants were asked to complete a Cyberball task that consisted of an alternating sequence of inclusion, exclusion, and overinclusion conditions.

Results Compared to healthy controls, participants with BPD reported higher levels of inner tension and more unpleasant emotions across all experimental conditions. At the neural level, the participants with BPD showed lower recruitment of the left hippocampus in response to social exclusion (relative to the inclusion condition) than the healthy controls did. Lower recruitment of the left hippocampus in this contrast was associated with childhood maltreatment in patients with BPD. However, this difference was no longer significant when we added the covariate of hippocampal volume to the analysis. During social overinclusion (relative to the inclusion condition), we observed no significant differences in a group comparison of neural activation.

Conclusions The results of our study suggest that patients with BPD experience more discomfort than do healthy controls during social interactions. Compared to healthy participants, patients with BPD reported more inner tension and unpleasant emotions, irrespective of the extent to which others included them in social interactions. At a neural level, the participants with BPD showed a lower recruitment of the left hippocampus in response to social exclusion than the healthy controls did. The reduced activation of this neural structure could be related to a history of childhood maltreatment and smaller hippocampal volume in patients with BPD.

Keywords Borderline personality disorder, Rejection sensitivity, Social exclusion, Social overinclusion, Cyberball paradigm, fMRI

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Background

Humans are motivated to engage in social interactions and develop and maintain social connections. A need to belong is fundamental; if this need is not met, it has a negative impact on well-being and mental health [1]. Social exclusion has been proposed as a psychosocial factor significantly contributing to the development and persistence of several mental disorders [2]. One of them is borderline personality disorder (BPD), characterized in part by a pattern of unstable interpersonal relationships and an intense fear of social exclusion [3].

The interpersonal difficulties of patients with BPD are closely related to the concept of rejection sensitivity. Previous research has shown that patients with BPD approach social situations with expectations of rejection that make them hypervigilant for signs of potential exclusion [4–6]. Once confronted with clues of potential rejection, patients with BPD tend to see those signs as more threatening and they experience more distress and anger than healthy controls do [5, 7]. Patients with BPD also tend to respond to actual or perceived rejection with maladaptive behavior, that may include self-mutilation, withdrawal, or hostile behavior [5, 8, 9]. Consistent with these results, a recent meta-analysis identified a moderate relationship between BPD and rejection sensitivity after correction for publication bias ($r = 0.338$, $p < 0.001$, number of included studies: 52). Patients with BPD had significantly higher sensitivity to rejection when compared with healthy controls ($r = 0.784$, $p < 0.001$, number of included studies: 12) as well as when compared with patients with other mental health conditions, including social anxiety disorder and current mood disorder ($r = 0.294$, $p < 0.01$, number of included studies: 12; [10]). In addition, there is a notable link between BPD, sensitivity to rejection, and maltreatment in childhood. According to the rejection sensitivity model proposed by Feldman and Downey [11], high rejection sensitivity is often associated with early experiences of social rejection by primary caregivers, including neglect or abuse. This may overlap with the invalidating environments often observed in the childhood of patients with BPD [12, 13].

Sensitivity to rejection has been studied with different experimental tasks. One of the most commonly used paradigms is a Cyberball game [14] that makes it possible to evaluate participant responses to social inclusion and exclusion. In this task, participants are asked to play a virtual ball-tossing game with two other players, and they are led to believe that they are interacting with real participants. However, the game is pre-programmed; depending on the condition, the actual participant either receives the same number of ball tosses as the other "players" (inclusion condition) or the participant does not receive the ball again after a few initial throws (exclusion condition).

Previous neuroimaging studies identified several brain regions that were involved in the neural processing of social exclusion in healthy participants. A recent meta-analysis that incorporated 53 Cyberball studies revealed increased activation in the bilateral ventral anterior cingulate cortex (vACC), right posterior insula, right superior frontal gyrus (SFG), left inferior frontal gyrus (IFG), left posterior cingulate cortex (PCC), and left occipital pole [15]. There has been some evidence of recruitment of the anterior insula and the dorsal anterior cingulate cortex (dACC; [16]). However, meta-analyses did not identify the involvement of these two regions in the neural processing of social exclusion [15, 17]. Although the precise mechanisms by which these regions are involved in social exclusion remain unknown, existing evidence suggests that increased activity in the vACC is associated with processing emotions and distress induced by social rejection [16, 18, 19]. Enhanced neural activity in the IFG and SFG is linked to the cognitive regulation of feelings after social exclusion [15, 16, 19]. Together with the PCC, the inferior and superior frontal gyri are thought to be related to mentalizing processes and autobiographical recollection [15, 20, 21].

Neuroimaging studies focusing on the neural substrates of social exclusion in patients with BPD have reported mixed results. In some Cyberball studies, participants with BPD showed increased activation in the pregenual anterior cingulate cortex (preACC; [22]), dorsomedial prefrontal cortex (dmPFC; [23]) and dorsolateral prefrontal cortex (dlPFC; [24]), premotor cortex (PMC; [23]), and precuneus [22], compared to healthy controls. On the other hand, Fertuck and colleagues [24] did not observe any significant differences between BPD patients and healthy controls in neural responses to exclusion events. However, they identified differences in modulation of this neural response through rejection distress. As the level of context-specific rejection distress increased, the response of the rostromedial prefrontal cortex (rmPFC) to exclusion events decreased in participants with BPD but not in healthy controls. The heterogenous results of neuroimaging studies could be explained by the different designs of the Cyberball task. While a majority of studies employed a block design [22–24], Fertuck and colleagues [25] used an event-related design with parametric modulation of exclusion probability. Although the mechanism by which these regions are involved in the processing of social rejection remains unknown, Rappaport and Barch [26] pointed out that the neural

response to social exclusion in BPD patients was associated mainly with increased activity of regions in the default mode network (DMN) and suggested that the hyperactivation of the DMN could be related to negative self-referential processing following social exclusion.

Moreover, growing evidence shows that in patients with BPD, the activation of regions involved in the neural processing of exclusion is increased even during social inclusion. Compared to healthy controls, patients with BPD showed higher neural activation within the anterior insula, dmPFC, dlPFC, PMC, and the precuneus when socially included (relative to passive watching; [4, 23, 27]). Increased activation in most of these regions was significant even in comparison with patients with nonsuicidal self-injury (NSSI; [4, 23]) and/or major depressive disorder (MDD; [27]). Differences in the cerebral processing of social inclusion are in line with the subjective feelings of rejection, higher levels of negative emotions, and lower sense of belonging that patients with BPD reported during inclusion conditions [5, 22, 24, 28].

Some evidence has suggested that patients with BPD need to be overincluded in social situations to experience a decrease in unpleasant emotions to a level comparable to that of healthy controls. During the overinclusion condition in the Cyberball paradigm, in which most of the ball passes are directed to the participant [14], patients with BPD reported reduced levels of negative emotions (relative to the inclusion condition). However, the feeling of social connection and the satisfaction of social needs did not differ between conditions and were significantly lower when compared with healthy controls [28, 29]. A recent EEG study examined the effects of social overinclusion on the event related potential P2, which has been linked with the processing of rewarding stimuli. In participants with BPD, the transition from inclusion to overinclusion was associated with an increase in the P2 amplitude, although the level of positive emotions did not differ between conditions [30]. Another EEG study focused on overinclusion and the P3 complex that is related to the processing of expectancy violation. Compared to healthy controls, patients with BPD showed enhanced P3 amplitudes in both the inclusion and overinclusion conditions [29]. Taken together, the results of these studies suggest that increases in the frequency of social interactions are processed as rewarding and lead to the reduction of painful emotions in patients with BPD. However, the effect of the overinclusion experience on positive emotions, satisfaction of social needs, and feelings of social connection might be limited. The experience of social overinclusion may be too brief for patients with BPD for it to affect their long-lasting and deep-seated expectations of rejection. As a result, social situations might be more uncomfortable for patients with BPD, regardless of the extent to which others include them in social interactions.

While the neural correlates of social exclusion and inclusion have been examined in several studies, the neural processing of social overinclusion has received little attention and remains underexplored. The aim of the present study was to gain further insight into the experience of social exclusion and overinclusion and its underlying neural processes in patients with BPD. We used the Cyberball paradigm with alternating blocks of three different conditions: social inclusion, social exclusion, and social overinclusion. As pointed out by Bolling et al. [31], the alternating design of the Cyberball task could eliminate potential confounds arising from scanner drift, motion, and changes in participant attention and fatigue over the course of the scanning session. The alternating Cyberball design also corresponds to naturally occurring social interactions, where the level of social engagement varies over time.

We hypothesized that participants with BPD would feel more inner tension and unpleasant emotions than healthy controls during both the exclusion and the inclusion conditions, but not during the overinclusion condition. At a neural level measured by functional magnetic resonance imaging (fMRI), we expected that the participants with BPD would show differential brain activation during the exclusion condition (relative to the inclusion condition) when compared with healthy controls. In line with previous studies using a similar design, we hypothesized that patients with BPD would show enhanced activation in ACC, dmPFC, and dlPFC during the social exclusion. We also expected that participants with BPD would exhibit distinct patterns of brain activation during the overinclusion condition (relative to the inclusion condition) when compared with healthy controls. We hypothesized that BPD patients would show decreased activation in areas associated with processing of social rejection during the overinclusion condition, as opposed to the inclusion condition.

Methods

Participants

This study involved 30 participants diagnosed with BPD (29 female and one male; age: $M = 24.2$, $SD = 5.2$) and 30 healthy controls (29 female and one male; age: $M = 24.7$, $SD = 5.3$) with no current or lifetime psychiatric diagnoses. Participants with BPD were recruited from outpatients receiving treatment at the Department of Psychiatry of the University Hospital Brno. They were

included in the study if they met at least five of the nine DSM-V criteria for BPD and had one or more suicidal behavior and/or NSSI episode in the past six months. Healthy controls were recruited through social media advertisements to match for gender, age, and the highest degree of education with the clinical group. Participants with psychotic disorder, autism spectrum disorder, severe neurological disorder, or any contraindication to fMRI scanning were excluded from the study.

In the clinical group, 28 of the 30 participants with BPD met the criteria for other mental disorders. The most prevalent co-occurring disorders were MDD (50%), substance use disorder (43.3%), social anxiety disorder (33.3%), posttraumatic stress disorder (PTSD, 23.3%), and panic disorder (20%). At the time of assessment, the participants with BPD were undergoing treatment with various kinds of antidepressants (66.7%), mood stabilizers (6.7%), benzodiazepines (26.7%), and antipsychotic medication (43.3%). Medication was not interrupted as the treatment of the participants with BPD was ongoing; however, all participants were asked not to take any sedative medication prior to fMRI scanning. Further details on sample characteristics are provided in Table 1.

Procedure

This study was part of a larger project focusing on neural mechanisms of dialectical behavior therapy in patients with BPD. The procedure was conducted in accordance with the Declaration of Helsinki, and it was approved by the Ethics Board of the Faculty of Medicine, Masaryk University, and by the Ethics Board of the University Hospital Brno. All participants agreed with their involvement in the study and provided written informed consent. At the first session, participants were asked to complete a set of self-report questionnaires and they underwent a semi-structured interview with a trained psychiatrist or psychologist working under supervision. The following fMRI session was combined with a simultaneous EEG measurement. During this session, participants completed several tasks, including the Cyberball paradigm. In this article, we present only the part relevant to

Table 1 Demographic and clinical characteristics of patients with BPD and healthy controls

	BPD-patients		**HC**		**BPD vs. HC**		
	N **= 30** **96.7% female**		***N*** **= 30** **96.7% female**				
	M	SD	M	SD	Independent t-test		
Age	24.2	5.2	24.7	5.3	t(57) = –0.40	*p* = .688	d = –0.11
BSL-23	51.7	14.0	5.7	5.6	t(36.77) = 16.54	*p* = < .001	d = 10.37
MADRS	24.7	7.1	0.8	1.1	t(30.40) = 18.358	*p* = < .001	d = 5.05
BDI	36.0	9.0	5.9	5.0	t(43.28) = 15.74	*p* = < .001	d = 7.31
BAI	25.4	8.1	5.9	4.3	t(43.25) = 11.50	*p* = < .001	d = 6.33
CTQ	58.1	13.4	32.4	5.8	t(37.87) = 9.51	*p* = < .001	d = 10.29
RSQ	15.3	4.9	6.5	2.9	t(57) = 8.33	*p* = < .001	d = 4.01
UPPS-P	132.0	19.7	81.5	14.4	t(57) = 10.98	*p* = < .001	d = 17.41
DERS	61.5	7.3	31.0	6.6	t(57) = 16.66	*p* = < .001	d = 7.02
Education	N		N		Mann–Whitney U test		
Primary	6		4		U = 310	*p* = .025	r = .31
Lower secondary	4		0				
Higher secondary	16		15				
University	4		11				
Comorbidity	N						
MDD	15						
PTSD	7						
Substance abuse	13						
Panic disorder	6						
Social anxiety	10						
OCD	4						

Note. *BPD* borderline personality disorder, *HC* healthy control, *N* number of participants, *M* mean, *SD* standard deviation, *BSL-23* Borderline Symptom List, *MADRS* Montgomery-Åsberg Depression Rating Scale, *BDI* Beck Depression Inventory, *BAI* Beck Anxiety Inventory, *CTQ* Childhood Trauma Questionnaire, *RSQ* Rejection Sensitivity Questionnaire, *UPPS-P* Impulsive Behavior Scale, *DERS* Difficulties in Emotion Regulation Scale, *MDD* major depressive disorder, *PTSD* posttraumatic stress disorder, *OCD* obsessive–compulsive disorder

processing social interactions. Other tasks and EEG data are not reported in this article.

Psychometric measurements

The diagnosis of BPD was verified by a trained psychiatrist or psychologist working under supervision using the Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5-PD; [32]). Severity of depressive symptoms was assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS; [33]), and information about the quantity and severity of suicidal behavior and NSSI episodes was obtained using a modified version of the semi-structured Suicide Attempt Self-Injury interview (SASII; [34]).

Participants were then asked to complete a set of self-report questionnaires. We assessed severity of BPD symptoms using the Borderline Symptom List (BSL-23; [35]; Czech version: [36]), depressive symptoms using the Beck Depression Inventory (BDI; [37]; Czech version: [38]), anxiety symptoms using the Beck Anxiety Inventory (BAI; [39]; Czech version: [40]), severity of different types of childhood trauma using the Childhood Trauma Questionnaire (CTQ; [41]), rejection sensitivity using the Rejection Sensitivity Questionnaire (RSQ; [42]), tendency to impulsive behavior using the Impulsive Behavior Scale (UPPS-P; [43]; Czech version: [44]) and emotion dysregulation using the Difficulties in Emotion Regulation Scale Short Form (DERS-SF; [45]).

Experimental task

We used the Cyberball task to examine the processing of social interactions in a laboratory setting [14]. Participants were asked to play a virtual ball-tossing game with two other players who were presented as being in another room. In reality, the game was pre-programmed, and participants played with a computer [14, 46]. Participants were represented by a hand at the bottom of the screen, and they could pass the ball to the other players by pressing a corresponding button. The two co-players were represented by animated figures with photographs and names, added to increase the ecological validity of the paradigm [14, 24].

In this study, we implemented the Cyberball task consisting of three different conditions: social inclusion, social exclusion, and social overinclusion. The task was divided into 15 rounds with 5 rounds per condition; each round lasted around 70 s and consisted of 12 throws. Experimental conditions were presented to participants in a pseudo-random order. In the inclusion condition, participants received the ball randomly in 70% of all throws. During the exclusion condition, participants received the ball only once at the beginning of the round and then they were excluded from the game for the remaining 11 throws. In the overinclusion condition, the computer-controlled players exchanged the ball between themselves only once at the beginning of the round and then they kept passing the ball to the participant for the remaining 11 throws.

After each round, participants were asked to indicate their subjective valence of emotional experience (5 points, ranging from *"very unpleasant"* to *"very pleasant"*) and the level of inner tension (5 points, ranging from *"not at all"* to *"very strong"*) on a visual rating scale.

Functional and structural MRI acquisition

The acquisition was performed on the Siemens Prisma 3 T MR whole-body scanner with 64-channel head-neck coil. A high-resolution structural T1 image was scanned for each participant. This makes it possible to localize the active brain areas more accurately. Parameters of the MPRAGE sequence were 240 sagittal slices, TR = 2300 ms, TE = 2.34 ms, FOV = 256 mm, flip angle = 8°, slice thickness = 1 mm. Functional blood-oxygen-level dependent (BOLD) MR data were acquired in a single scanning session with a T2*-weighted multiecho multiband echo planar imaging (ME MB EPI) sequence of 1250 scans (60 slices, TR = 1000 ms, TE = 14, 34.63 and 55.26 ms, FOV = 200 mm, flip angle = 50°, slice thickness = 2.5 mm, MB factor = 5). TE values were chosen according to recommendations for ME EPI [47], where the second echo was very close to the typical value of single echo acquisition.

Data analysis

Behavioral and self-reported data

Behavioral and self-reported data analysis was performed in Jamovi software version 2.3 [48]. Differences in self-report questionnaires were analyzed by independent t-tests. Differences in ratings of inner tension and valence of emotional experience reported after each block of the Cyberball game were tested by mixed analysis of variance (ANOVA) with the between-subject factor "group" (BPD and HC) and the within-subject factor "Cyberball condition" (exclusion, inclusion, and overinclusion). Post hoc comparisons using Tukey correction were computed to explore the differences motivating the main effects.

fMRI data pre-processing

The data were processed with the SPM12 toolbox [49] running under MATLAB R2021a [50]. At first, the realignment procedure was performed to the middle echo scans (all middle echo scans were aligned to the first middle echo scan). The same translations and rotations were used for other echoes. Physiological noise linked to the ECG and respiration were suppressed by RETROICOR in all scans. Composite scans generated

from all three echoes were created using the contrast-to-noise weighted average. In each voxel, temporal SNR (tSNR) values were computed for each echo. The resulting voxel value was given by the weighted average of the three original tSNR-weighted values and echoes [51, 52]. The processed functional scans were then co-registered to anatomical scans and all data were normalized to the Montreal Neurological Institute (MNI) template. As a last step, the spatial smoothing of functional data was calculated by Gaussian filter with full width at half maximum (FWHM) of 5 mm. The data quality was checked for the presence of spatial abnormalities in Mask Explorer [53] and for the presence of excessive movement in the movement_info tool [54]. Movement in the data was controlled by a framewise displacement (FD) measure [55]. All the participants were eligible using the thresholds of 20% of scans exceeding FD = 0.5 mm and 1% of scans exceeding FD = 1.5 mm [51].

fMRI data analysis

General linear modelling (GLM) was used on the pre-processed data in SPM12 [49]. In the first step, GLM was performed on the subject level. The design matrix contained five time-courses of stimulation design convolved with canonical hemodynamic function and six confound regressors for movement (translations and rotations from the realignment pre-processing procedure). The stimulation task was modelled as a block design, where five time-courses of stimulation represent exclusion blocks, inclusion blocks, overinclusion blocks, a fixating cross screen preceding each round, and a resting block that comes after each round. First level contrasts correspond to condition blocks. In the next step, group-level GLM analysis was performed. According to our hypotheses, we used a two-sample paired t-test to find the differences between exclusion > inclusion and overinclusion > inclusion conditions in both subject groups. To compare these contrasts between subject groups, a flexible factorial design was used. The factors of subject group, condition, and their interactions were modelled. The interaction group and condition were then contrasted. Group results were evaluated with cluster level inference at p (FWE) < 0.05 (with initial cutoff at $p < 0.005$). The results were visualized using xjView toolbox [56].

Correlation analyses

The peak MNI coordinate was selected based on fMRI activations. Data for each subject were extracted as the mean of a 5-mm radius sphere around this coordinate. Pearson correlation coefficients were then calculated between activations in the region of interest and clinical scales or self-reported data. In the case of dichotomous variables, logistic regression was used.

Results

Self-reported results

The statistical analysis of self-report measures revealed significant differences between the groups (Table 1). Compared to healthy controls, participants with BPD showed significantly higher severity of BPD symptoms, depression, and anxiety. They also reported significantly higher sensitivity to social rejection, higher emotion dysregulation, and a higher tendency to impulsive behavior.

Behavioral results

The statistical analysis revealed a significant main effect of group on the valence of emotional experience reported after each block of the Cyberball task, F(1, 58) = 15.5, p = < 0.001, $\eta^2 = 0.141$. Compared with healthy controls, participants with BPD reported more unpleasant emotions across all experimental conditions, t(58) = -3.94, $p_{tukey} = < 0.001$. There was also a significant main effect of condition on the valence of emotional experience, F(1.49, 86.67) = 30.54, $p = < 0.001$, $\eta^2 = 0.113$. Post hoc comparisons revealed that the exclusion condition was associated with a more unpleasant emotional experience than the inclusion and overinclusion conditions, t(58) = -5.57, $p_{tukey} = < 0.001$, respectively t(58) = -6.32, $p_{tukey} = < 0.001$. The valence of emotional experience during the inclusion condition did not significantly differ from the overinclusion condition, t(58) = -1.01, $p_{tukey} = 0.576$. There was no significant interaction effect between group and condition, F(1.49, 86.67) = 1.55, $p = 0.221$. Descriptive statistics and estimated marginal means plots are provided below (Table 2 and Fig. 1.A.).

Regarding inner tension (Table 2 and Fig. 1.B.), there was a significant main effect of group, F(1, 58) = 14.0, $p = < 0.001$, $\eta^2 = 0.164$. Participants with BPD experienced increased inner tension across all experimental conditions when compared with healthy controls, t(58) = 3.75, $p_{tukey} = < 0.001$. The statistical analysis revealed a significant main effect of condition, F(1.68, 97.44) = 15.48, $p = < 0.001$, $\eta^2 = 0.032$. Post hoc comparisons showed that the exclusion condition was associated with a significantly higher level of inner tension than the inclusion and overinclusion conditions, t(58) = 4.353, $p_{tukey} = < 0.001$ respectively t(58) = 4.382, $p_{tukey} = < 0.001$. The difference between the inclusion and overinclusion conditions was not significant, t(58) = 0.459, $p_{tukey} = 0.891$. There was no significant interaction effect between group and condition, F(1.68, 97.44) = 1.06, $p = 0.341$.

Table 2 Average ratings of valence of emotional experience and inner tension after exclusion, inclusion, and overinclusion conditions in a Cyberball task

Ratings		Cyberball condition		
		Exclusion	Inclusion	Overinclusion
Valence of emotional experience	BPD	M = 2.31	M = 3.09	M = 3.17
		SD = .71	SD = .76	SD = .77
	HC	M = 3.22	M = 3.72	M = 3.76
		SD = .89	SD = .96	SD = .87
Inner tension	BPD	M = 3.17	M = 2.66	M = 2.64
		SD = 1.09	SD = .97	SD = 1.04
	HC	M = 2.15	M = 1.86	M = 1.82
		SD = .86	SD = 1.00	SD = .95

Note. *BPD* borderline personality disorder, *HC* healthy control, *M* mean, *SD* standard deviation; valence of emotional experience (5 points, ranging from 1 = "very unpleasant" to 5 = "very pleasant"); the level of inner tension (5 points, ranging from 1 = "not at all" to 5 = "very strong")

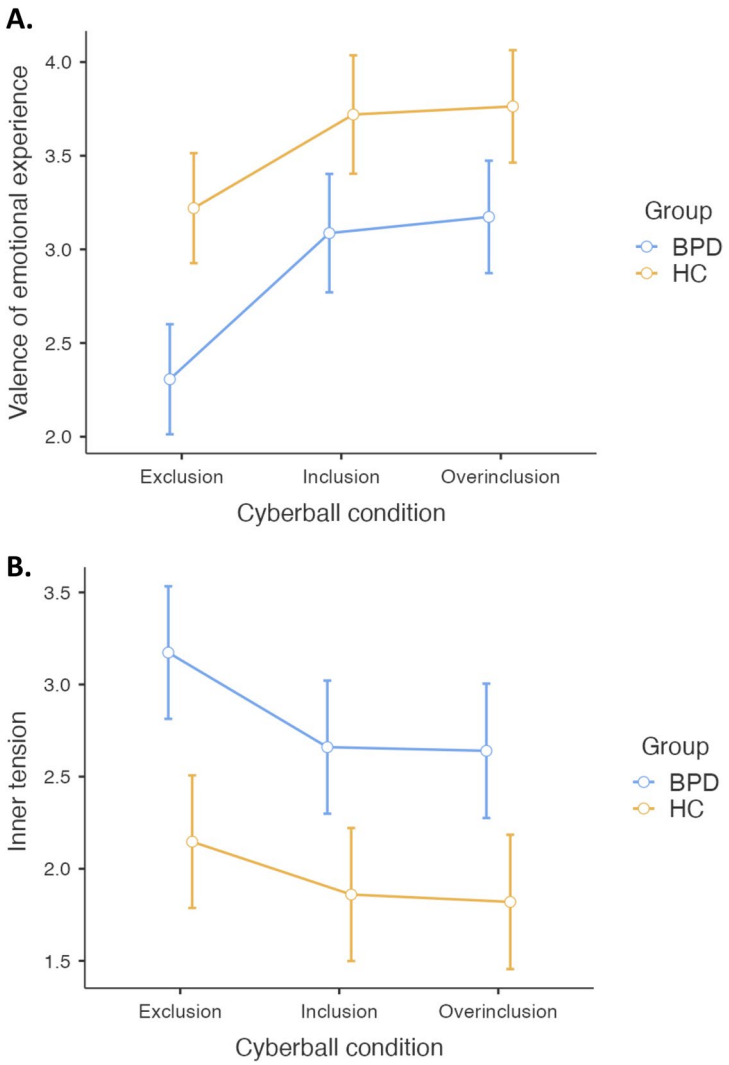

Fig. 1 Estimated marginal means plots show average ratings of (**A**) valence of emotional experience and (**B**) inner tension after exclusion, inclusion, and overinclusion conditions reported by participants with BPD (blue) and healthy controls (yellow). *Note*. BPD = borderline personality disorder; HC = healthy control; valence of emotional experience (5 points, ranging from 1 = "very unpleasant" to 5 = "very pleasant"); the level of inner tension (5 points, ranging from 1 = "not at all" to 5 = "very strong"); error bars represent 95% confidence interval

fMRI results

Exclusion compared to inclusion

The healthy controls showed increased engagement during the exclusion condition as compared to the inclusion condition within two clusters: one cluster comprising the left superior, middle, and inferior temporal gyri (STG, MTG and ITG) and the other cluster encompassing the left middle and inferior frontal gyri (MFG and IFG). The BPD group showed increased engagement within the cluster including the left superior and middle occipital gyri.

When comparing participants with BPD with healthy controls, we did not find any significant increase of neural activation in the participants with BPD; however, we observed enhanced neural reactivity within the left hippocampus in healthy controls during the social exclusion condition relative to the social inclusion condition. Table 3 and Fig. 2 show significant results of the exclusion to inclusion contrast together with the cluster characteristics. Figure 1 in the supplementary material displays the distribution of Cohen's d for each contrast.

Examination of the hippocampal volume influence

Since previous studies found difference in hippocampal volume between patients with BPD and healthy controls [57, 58], we performed several additional analyses to examine whether the difference in neural activation within the left hippocampus was associated with the volume of the structure. First, we calculated the rank sum test that confirmed a significant difference between participants with BPD and healthy controls in the volume of the left hippocampus (rank sum = 730, U = 265, $p = 0.03$). Second, we added the covariate of hippocampal volume to the analysis of task-related activation. The results of this supplementary analysis did not find significant difference between participants with BPD and healthy controls in neural responses to social exclusion relative to social inclusion. A detailed description of the additional analyses can be found in the supplementary material.

Overinclusion compared to inclusion

We did not find any significant neural activation when comparing the overinclusion and inclusion conditions in participants with BPD or in healthy controls. Similarly, we did not observe any significant differences in a group comparison of neural activation during the overinclusion condition as compared to the inclusion condition.

Correlation analyses

We conducted a correlation analysis to examine the association between enhanced neural activation within the left hippocampus and behavioral data and psychometric measurements. In healthy controls, neural activation within the left hippocampus was significantly negatively correlated with BSL-23 behavioral scores (r = -0.440; $p = 0.015$) and BDI scores (r = -0.400; $p = 0.027$). In participants with BPD, we observed a significant negative correlation between neural activation in the left hippocampus and CTQ scores (r = -0.37; $p = 0.05$).

We also performed additional correlation analysis to examine the potential association between hippocampal volume and psychometric measurements. No significant correlations were observed in patients with BPD or healthy controls.

Discussion

The present study aimed to gain further insight into the experience and the cerebral processing of social interactions in patients with BPD by using fMRI during

Table 3 Enhanced neural activation during exclusion compared to inclusion conditions in the Cyberball paradigm. Statistically significant results (p (FWE) < .05 for cluster-level inference, k > 10 voxels) for HC, patients with BPD and comparison between the groups (HC vs. BPD)

	Anatomic label	Side L/R	MNI			Cluster size	$P_{FWE-cor}$	Cohen's d
			x	y	z			
HC	Superior temporal gyrus	L	-48	8	-29	107	.015	0.75
	Middle temporal gyrus							
	Inferior temporal gyrus							
	Middle frontal gyrus	L	-42	29	-8	147	.002	0.59
	Inferior frontal gyrus							
BPD	Superior occipital gyrus	L	-12	-94	4	82	.029	0.49
	Middle occipital gyrus							
HC vs. BPD	Hippocampus	L	-24	-10	-20	118	.008	1.05

Note. *BPD* borderline personality disorder, *HC* healthy control, *L* left, *R* right, *MNI* Montreal Neurological Institute (x, y and z coordinates are provided in mm); Cluster size = number of voxels

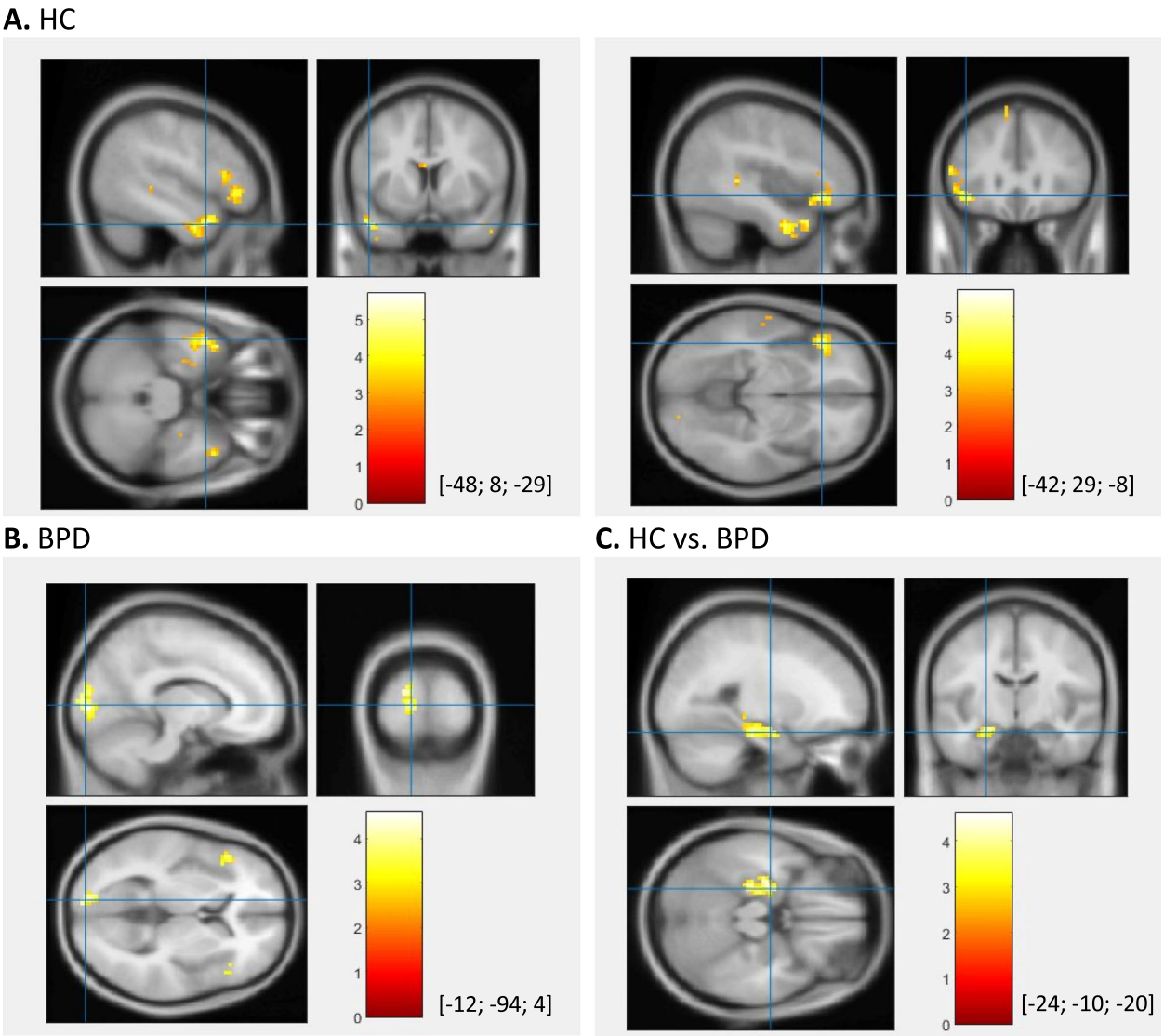

Fig. 2 Enhanced neural activation during exclusion compared to inclusion conditions in the Cyberball paradigm. Statistically significant results (p (FWE) < .05 for cluster-level inference, k > 10 voxels) for healthy controls (**A**), patients with BPD (**B**) and comparison between the groups (HC vs. BPD; **C**). Intersection of blue lines indicates the peak of each cluster, MNI-coordinates are provided in the squared brackets. *Note.* BPD = borderline personality disorder; HC = healthy control; MNI = Montreal Neurological Institute (x, y and z coordinates are provided in mm)

experimentally induced experiences of social exclusion, inclusion, and overinclusion. Compared to healthy controls, participants with BPD reported higher levels of inner tension and more unpleasant emotions across all experimental conditions. At a neural level, participants with BPD showed lower recruitment of the left hippocampus in response to social exclusion (relative to the inclusion condition) when compared to healthy controls. Lower recruitment of the left hippocampus in this contrast was associated with childhood maltreatment in patients with BPD. However, the difference in the left hippocampal activity between the groups was no longer significant when we added the covariate of hippocampal volume to the analysis. During social overinclusion (relative to the inclusion condition), we did not observe any significant differences in the group comparison of neural activation.

In line with our expectations, during social exclusion and inclusion the participants with BPD experienced higher levels of inner tension and more unpleasant emotions than the healthy controls. These findings are consistent with previous research in which patients with BPD indicated stronger feelings of social rejection, a lower sense of belonging, and more unpleasant emotions during both exclusion and inclusion conditions than did healthy controls [5, 19, 21, 24]. Nevertheless, our initial

assumptions regarding social overinclusion were not confirmed. Prior studies of participants with BPD associated overinclusion with a reduction of unpleasant emotions to a level comparable with that of healthy controls. In our study, however, patients with BPD reported increased inner tension and more unpleasant emotions even after experiences of social overinclusion. The mixed results could be partly explained by the different designs of the Cyberball task. Previous studies either applied only the inclusion condition followed by the overinclusion condition [29] or randomly assigned participants into groups with different degrees of social participation [28]. In this study, we used an alternating sequence of the exclusion, inclusion, and overinclusion condition. There is a possibility that the experience of social exclusion may have reduced reward processing and diminished the effect of overinclusion. In fact, similar results were observed in a study with healthy participants who experienced social exclusion, inclusion, and overinclusion during a continuous block of a Cyberball task with an event-related design [19]. Another possible explanation is that the experimentally induced overinclusion may have been too brief for the participants with BPD to affect their deep-seated anticipation of social exclusion. As patients with BPD approach social situations with the expectation of rejection [4, 6] and tend to perceive others as less trustworthy [59, 60], social situations may be more uncomfortable for them, regardless of the extent to which others include them in social interactions.

At a neural level, the healthy participants showed exclusion-evoked neural activation within the cluster comprising the left STG, MTG, and ITG and the cluster including the left MFG and IFG. These areas have previously been reported in other studies using the Cyberball paradigm in nonclinical populations [15, 31]. The activation of these regions during social exclusion could be linked to affective response and cognitive regulation of feelings of rejection [15, 17, 31]. On the other hand, participants with BPD showed increased engagement within the cluster including the left superior and middle occipital gyri during the exclusion condition. Previous studies focusing on social exclusion in BPD patients have not identified enhanced activation in this area. However, increased neural activation in this region has been observed during social exclusion in healthy participants [15] and has functionally been related to visual processing [61].

Although the participants with BPD experienced more discomfort than the healthy controls across all experimental conditions, these differences were not evident at the neural level. In contrast to our expectations, we did not observe any enhanced activation in the participants with BPD during social exclusion when compared to healthy controls. While some of the prior Cyberball studies identified exclusion-evoked activity within the preACC, dmPFC, dlPFC and precuneus in patients with BPD [22–24], our study did not replicate these findings. However, our results are in line with findings of the recent Cyberball study [25], which used an event-related design with parametric modulation of exclusion probability. Authors of this study did not observe any significant differences between BPD patients and healthy controls in neural responses to exclusion events. However, they identified atypical modulation of the rmPFC response by rejection distress in participants with BPD. Furthermore, our study did not identify any difference between patients with BPD and healthy controls in response to the overinclusion vs. inclusion conditions. Although the level of inner tension and unpleasant emotions was constantly higher in participants with BPD, both groups showed similar neural responses to social overinclusion.

A possible explanation for the lack of more pronounced neural responses to social exclusion and overinclusion could be the alternating design of the Cyberball task. In our study, we used a Cyberball design with alternating blocks of different experimental conditions to eliminate potential confounds arising from scanner drift, motion, and changes in participant engagement over the course of an fMRI session. The meta-analyses comparing traditional and alternating Cyberball designs with healthy participants did not confirm any significant differences between these two approaches [15, 17]. However, some authors have noted the risk of a "spill-over" effect associated with the alternating Cyberball version. They argue that the alternating design could potentially reduce neural differences between the experimental conditions, as the neural response to one condition might affect cerebral processing of other conditions in subsequent blocks [17]. Although the transfer effect has been reported even in studies using a traditional Cyberball design [62], the alternating approach with shorter blocks and repeated switches between different conditions could be more prone to this unintended effect.

Another factor that may have influenced our findings is using social inclusion as the control condition. Although it is a common approach in Cyberball studies [2, 15], some authors question whether the contrast between exclusion and inclusion represents the appropriate way to describe the brain regions that respond specifically to social exclusion [25, 26]. They point out that the interpretation of this contrast is problematic, as it is difficult to separate the specific effects of social exclusion from more general effects associated with processing of social stimuli (e.g. working memory, motor planning or sensory processing; [25]). The same question applies to the contrast between the inclusion and overinclusion conditions.

The authors suggest that a better option might be to use a neutral control condition, such as passively watching the game [26], or implementing the event-related design of the Cyberball paradigm [25].

Contrary to our expectations, participants with BPD differed from healthy participants in the activation of the hippocampus during the social exclusion condition. More precisely, compared to healthy controls, participants with BPD showed lower recruitment of the left hippocampus in response to the exclusion vs. inclusion condition. This result was quite surprising, as previous studies of patients with BPD have not reported reduced neural activation in this region. However, there is some evidence for increased hippocampal activation during social exclusion in healthy adult participants [31] and healthy children and adolescents [63]. Since the hippocampus plays an important role in learning, memory encoding and consolidation and emotional processing [64–66], it could be hypothesized that its increased activation reflects healthy participants' attempts to downregulate painful emotions after social rejection.

Another possible explanation for the lower recruitment of the left hippocampus during social exclusion could be reduced hippocampal volume amongst the participants with BPD. An association between a lower volume of hippocampus and BPD has been reported by several volumetric studies [57, 58]. Existing evidence suggests that the smaller hippocampus size is closely linked to experiences of childhood maltreatment [67–69], which is very common in patients with BPD [70]. In fact, 96.7% of participants with BPD in our study reported some form of childhood maltreatment. Based on these findings, we decided to include hippocampal volume in our additional analysis. In line with previous studies, our results showed that participants with BPD had a reduced volume of the left hippocampus in comparison with the healthy controls. When we added the covariate of hippocampal volume to the analysis of neural response to social exclusion, the difference in neural activation between the groups was no longer significant. These findings suggest that the previously observed lower recruitment of the left hippocampus during social exclusion in patients with BPD could partly reflect a reduced hippocampal volume in this group. Although there is not yet a clear explanation for a smaller hippocampus in patients with BPD, existing evidence suggests that the reduced volume could be associated with long-term differences in the activation of the hippocampal structure in patients with BPD. It also could be linked with impaired feedback inhibition of the hypothalamus–pituitary–adrenal axis and long-term alteration of cortisol levels in participants with BPD [71–73].

Although we did not observe any significant link between hippocampal volume and traumatic experiences during childhood, results of our correlational analysis revealed an association between exclusion-evoked neural activation of the left hippocampus and the childhood maltreatment in patients with BPD. These findings suggest that the initially observed reduced neural activation of the left hippocampus in BPD patients could be partly related to the history of childhood maltreatment. More research is needed to better understand the role of the hippocampus in processing social exclusion in BPD patients. Given the high prevalence of childhood maltreatment in this clinical population, future studies with BPD patients should focus on hippocampal neural activation as well as the volume of this structure.

Several limitations of the present study need to be addressed. As mentioned above, the alternating Cyberball design could potentially lead to reduced neural differences between the conditions, as it may be more prone to a transfer effect than the traditional Cyberball design. Another shortcoming is the absence of a neutral condition in the Cyberball paradigm; this made it difficult to separate task-specific from non-task-specific cognitive processes and prevented us from investigating the neural response to social inclusion. A neutral condition like passively watching the game could represent a better control condition for social exclusion and overinclusion. Nor did our study include a measure of the feeling of social connection and the satisfaction of social needs, which prevented us from capturing potential changes in these variables. There are also a few limitations related to the characteristics of our sample. As our study included mainly female participants (96.7%), our results cannot be easily generalized to male patients with BPD. Consistent with the high prevalence of comorbidity in patients with BPD, 93.3% of the patients in our study met criteria for another mental health condition (most prevalent co-occurring disorders were MDD, substance use disorder, social anxiety, and PTSD). We cannot rule out the potential effects of comorbid disorders on the neural processing of social interactions, as we did not include a clinical control group in this study. In addition, most of the participants with BPD were treated with various types of medication. This could reduce the differences between groups; however, a recent review of the existing literature found little or no effect of pharmacological treatments on the neural processing of emotional tasks in patients with BPD [74].

Conclusions

To conclude, the results of our study suggest that patients with BPD experience more discomfort than healthy controls during social interactions. Compared to healthy participants, patients with BPD reported

more inner tension and unpleasant emotions, irrespective of the extent to which others included them in social interactions. At a neural level, the participants with BPD showed a lower recruitment of the left hippocampus in response to social exclusion than the healthy controls did. The reduced activation of this neural structure could be related to a history of childhood maltreatment and smaller hippocampal volume in patients with BPD.

Abbreviations

ANOVA	Analysis of variance
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BOLD	Blood-oxygen-level dependent
BPD	Borderline personality disorder
BSL-23	Borderline Symptom List
CTQ	Childhood Trauma Questionnaire
dACC	Dorsal anterior cingulate cortex
DERS-SF	Difficulties in Emotion Regulation Scale Short Form
dlPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
dmPFC	Dorsomedial prefrontal cortex
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EEG	Electroencephalogram
FD	Framewise displacement
fMRI	Functional magnetic resonance imaging
FOV	Field-of-view
FWE	Family-wise error
FWHM	Full width at half maximum
GLM	General linear modelling
HC	Healthy control
IFG	Inferior frontal gyrus
ITG	Inferior temporal gyrus
L	Left
M	Mean
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	Major depressive disorder
ME MB EPI	Multiecho multiband echo planar imaging
MFG	Middle frontal gyrus
MNI	Montreal Neurological Institute
MTG	Middle temporal gyrus
N	Number of participants
NSSI	Nonsuicidal self-injury
OCD	Obsessive–compulsive disorder
PCC	Posterior cingulate cortex
PMC	Premotor cortex
preACC	Pregenual anterior cingulate cortex
PTSD	Posttraumatic stress disorder
R	Right
rmPFC	Rostromedial prefrontal cortex
RSQ	Rejection Sensitivity Questionnaire
SASII	Suicide Attempt Self-Injury Interview
SCID-5-PD	Structured Clinical Interview for DSM-5 Personality Disorders
SD	Standard deviation
SFG	Superior frontal gyrus
STG	Superior temporal gyrus
TE	Time to echo
TR	Repetition time
tSNR	Temporal signal-to-noise ratio
UPPS-P	Impulsive Behavior Scale
vACC	Ventral anterior cingulate cortex

Supplementary Information

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Additional file 1: Figure 1. Distribution of Cohen's d calculated voxel-wise in an exclusion vs. inclusion condition for each contrast: healthy controls (A), patients with BPD (B) and comparison between the groups (HC vs. BPD; C).

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Authors' contributions
A.L., M.R., M.J. and P.B. worked on the recruitment of participants. A.D., M.R. and P.T. conducted the clinical interviews. H.V. and K.Š. accompanied participants to fMRI measurements. M.L. programmed the fMRI stimulation and analyzed the fMRI data. A.L. with the help of P.L. analyzed the behavioral and self-report data. E.B. performed analyses to examine the association between task-related activation and hippocampal volume and helped with the interpretation of the results. P.L. and T.K. aided in interpreting the results and supervised the work. A.L. wrote the manuscript with the help of M.L., M.J., P.L. and A.D. All authors read and approved the final manuscript.

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Availability of data and materials
The data that support the findings of this study are not publicly available due to reasons of sensitivity, but they are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The procedure was conducted in accordance with the Declaration of Helsinki, and it was approved by the Ethics Board of the Faculty of Medicine, Masaryk University, and by the Ethics Board of the University Hospital Brno. All participants agreed with their involvement in the study and provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Publisher's Note

3.3 Indications from fMRI studies for the treatment of BPD

Current fMRI studies provide strong support for the central role of emotion dysregulation in BPD, particularly through amygdala hyperactivation and hypoactivation of the dorsolateral prefrontal cortex (DLPFC). Further, social situations appear to be experienced as more distressing by patients with BPD than by healthy individuals. Meta-analytic studies further indicate increased activation of the default mode network in patients with BPD, a finding consistent with heightened self-referential processing and a tendency to interpret social situations through a highly personalized lens from clinical practice. Further, trauma history appears to be an important factor influencing neural processing in BPD, as reflected by reduced hippocampal volume and altered hippocampal responses during experiences of social exclusion. Taken together, these findings suggest that effective treatment of BPD should focus on strengthening adaptive emotion regulation skills, enhancing prefrontal regulatory functions, addressing the consequences of traumatic experiences, improving social-cognitive and interpersonal skills, and helping patients evaluate social situations more accurately on the basis of contextual information and the perspectives of others, rather than relying predominantly on self-referential interpretations.

4 Targeted treatments of borderline personality disorder

Based on the findings of our previous research projects, we sought to implement and evaluate several treatment approaches for patients with BPD that specifically target emotion regulation abilities and their associated neural correlates, which represent a central dimension of the disorder. Dialectical behavior therapy (DBT) is a comprehensive psychotherapeutic treatment designed for individuals with severe emotion and behavioral dysregulation. Its primary goals are to reduce maladaptive behaviors while simultaneously enhancing emotion regulation capacities and interpersonal effectiveness skills. Section 4.1 outlines the fundamental principles and strategies of DBT and describes the DBT program implemented at our department. Annex 8 (Theiner, Linhartová, & Látalová, 2021) presents the first comprehensive introduction to DBT published in the Czech language, while the results of the effectiveness evaluation of our DBT program are currently under review. Section 4.2 introduces the innovative method of fMRI neurofeedback and summarizes current evidence regarding its use for improving emotion regulation in patients with BPD. Annex 9 (Linhartová et al., 2019) presents our highly cited systematic review of fMRI neurofeedback in emotion regulation conducted in international collaboration. Finally, Section 4.3 describes the application of repetitive transcranial magnetic stimulation (rTMS) as a method for enhancing

emotion regulation and reducing impulsivity in BPD, including the behavioral and neural findings from our study of prefrontal rTMS in patients with BPD. Annex 10 (Svěrák, Linhartová et al., 2022) presents a study of the behavioral and neural effects of rTMS in patients with BPD conducted at our department.

4.1 Dialectical behavior therapy

Dialectical behavior therapy (DBT) was developed by American psychologist Marsha M. Linehan who summarized the therapeutical approach in her book "Cognitive-Behavioral Treatment of Borderline Personality Disorder" in 1993 (Linehan, 1993). Linehan herself suffered from BPD and her story shows that BPD can indeed be effectively treated. She has summarized her experience and DBT development in her memoir (Linehan, 2020). Since then, DBT became one of the most widely used evidence-based treatments targeted at patients with severe emotional and behavior dysregulation who self-harm and are chronically suicidal. DBT is a team-based integrative outpatient psychotherapy program in standard length of 6 months to 1 year for the first stage of therapy which aims at behavioral stabilization. In several randomized controlled studies, DBT has been shown to decrease suicidal behavior and self-harming in patients with DBT, as well as other BPD symptoms (DeCou, Comtois, & Landes, 2019; Stoffers-Winterling, Völlm, Rücker, Huband, & Lieb, 2013).

4.1.1 Principles of DBT

DBT is based on integration of cognitive behavioral therapy and philosophy of dialectics and acceptance rooting from Zen Buddhism. Dialectics in DBT is a way of thinking, understanding the world, and communication that stems from the proposals that everything in the world has an opposite side and that we are all interconnected in some way. Practically, dialectical thinking means that there are multiple perspectives of how things and situations can be perceived, rather than one ultimate truth, and that the effective way of understanding ourselves and the others is to try and look at things or emotions from different viewpoints. Dialectics is a direct way of working with black-and-white thinking, fluctuation between extremes, and splitting in patients with BPD. It leads us to being able to approach life flexibly according to what is effective for the given person in the given situation. Dialectics also leads us to balance between extremes which has direct impact on the therapy. DBT is a balance between acceptance and change, between caring and demanding, and much more.

Another crucial principle of DBT is non-judgement. All humans have a natural tendency to judge which means adding a subjective interpretation to the facts that are happening to us and around us. Although judgement is sometimes necessary or even beneficial, it often leads to negative emotions or worsens relationships (towards ourselves and towards other people) and typically does not promote change. This is especially the case when people believe their judgements are facts, and not a subjective point of view. Negative judgements often stem from

inability to understand another point of view (i.e., failure of dialectics) and also lead to stigmatization. Instead, DBT assumes that all behaviors are caused, all behaviors make sense from some point of view, and understanding and changing the causes of our behavior is more effective than judging and blaming.

DBT uses the method of behavioral analysis to understand causes, functions and consequences of patients' maladaptive behaviors, including self-harming and suicidal behaviors which are the primary focus of DBT first stage of therapy, and which typically serve as a way of emotion regulation, while patients do not have effective skills for managing their emotions. The overreaching goal of DBT is to help patients to have a life worth living. The main way of approaching this goal in DBT, is to help the patients in achieving their individual life goals and, at the same time, decrease problem behaviors which prevent the patients from achieving their life goals, while constantly balancing acceptance and change in a non-judgmental way.

DBT is a team-based treatment which means that a team of professionals work together in patients' therapy. While each patient has his own individual therapist, he meets with other therapists in group training which is focused on learning new skills. The team also serves as a mean of increasing support, motivation, model adherence, and therapy effectiveness of the therapists. Relationship between therapist and patient is a crucial basis of DBT and the goal is to build a strong and respectful relationship which will help the patients to achieve changes in their life.

4.1.2 Modules and functions of comprehensive DBT

Although some parts and principles of DBT can be effectively used outside of a full DBT program, the comprehensive DBT which is evidence-based for treatment of patients with severe emotional and behavior dysregulation constitutes from four modules and five functions.

The first module is individual therapy which is delivered for one hour per week in standard. In individual therapy, the therapist and the patient work on individual behaviors, problems, and goals of the patient, while the primary focus is on decreasing behaviors that can kill the patient (self-harming and suicidal behavior) or destroy therapy (preventing dropout, absence and other obstacles that decrease therapy effectiveness). At the same time, we are working on achieving patients' life goals and implementing their new skills into their life. Primary function of the individual therapy is increasing patient motivation.

The second module is skills training which is delivered to a group of patients led by two therapists and is delivered for 2.5 hours per week in standard. The function of this module is to teach patients new and effective skills in four areas: mindfulness, distress tolerance, emotion regulation, and interpersonal effectiveness. The focus is on practical training of the new skills and their implementation into the patients' real lives.

The third module is phone coaching which is available 24/7 and typically provided by individual therapist of each patient. Patients can call for coaching whenever they encounter a situation in which they are trying to use their new skills, and they need help with it. Phone coaching are short calls focused on skills enhancement in the given situation. Although patients can call any time, the therapists answer the calls within their individual time and personal limits. The primary function of this module is skills generalization, another function is to promote patients' ability to ask for help effectively and before maladaptive behavior. From this reason, patients cannot use the phone coaching 24 hours after they have self-harmed while, at the same time, every reasonable effort is given from the therapists to help the patients before they would engage in self-harming behavior.

The fourth module is consultation team of therapists. The therapeutical team meets at a given time of week for 1 to 1.5 hour per week and every week. The function of this module is to increase the therapists' motivation and effectiveness in therapy. Therapy with suicidal patients often brings painful emotions and difficult situations for the therapists as well and many therapists burn out or exclude these patients from treatment. Consultation team serves as prevention for these problems, and thus enhances the therapy effectiveness.

The fifth basic function of DBT is establishing a structure which is often highly needed in patients' unstable lives. Structure is delivered through the structure of therapy and its modules itself, helping the patients with self-monitoring and establishing a structure of their daily lives and other means.

4.1.3 Implementing DBT in Czech Republic

Given its longer than 30-year history, DBT is no new treatment. However, it was almost unknown up to the recent years in Czech Republic. The first DBT program in Czech Republic was established in 2015 in a social services organization called "Kaleidoskop" by Renata Tumlířová. Kaleidoskop currently provides outpatient and community based DBT program as well as DBT program for adolescents and their families. Early in my career, I realized that effective treatments targeted on patients with BPD are lacking in the Czech Republic and that stigmatization of these patients among professional is high. Luckily, I was not alone with the idea of implementing DBT at our workplace, and we formed a DBT team at the Department of Psychiatry of the University Hospital Brno thanks to the support of the head of our clinic and my research supervisor professor Tomáš Kašpárek. Our team underwent intensive training in DBT in Great Britain with British Isles DBT training and we started our DBT program in September 2019. Since then, we continuously improve our DBT services, over 130 patients successfully underwent our program, and we provide educational DBT workshops for our staff as well as across the Czech Republic. Another DBT program with trained therapist was developed in Child Psychiatric Hospital Opařany. The three mentioned organizations formed the first Czech professional organization as a DBT section of Czech association for cognitive behavioral therapy in 2023. We are together working on bringing Czech DBT literature

translations, development of Czech DBT training and we became a member of newly established European DBT Association (which is a member of the World DBT Association). Further, five new DBT teams were established during the past three years thanks to the project called "Gradient" of National Institute for Mental Health in which I served as expert guarantor, and our professional organization includes more than 70 trained therapists. As a result of these efforts, we have succeeded in building a growing Czech DBT community that is closely connected with experienced international colleagues. Consequently, DBT is gradually becoming a more widely recognized and accessible treatment option for patients with BPD in the Czech Republic. These developments represent a substantial improvement in the availability of evidence-based care for individuals with BPD and exemplify the successful translation of our research activities into direct clinical practice.

Annex 8

Theiner, P., **Linhartová, P., &** Látalová, A. (2021). Dialectical behavioral therapy; [DIALEKTICKA BEHAVIORALNI TERAPIE]. Psychoterapie, 15(1), 23–29. ISSN 1802-3983. Available at: https://journals.muni.cz/psychoterapie/article/view/14209

DIALEKTICKÁ BEHAVIORÁLNÍ TERAPIE

Dialectical Behavior Therapy

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ABSTRAKT

Dialektická behaviorální terapie (DBT) byla vytvořena jako komplexní program pro klientky s hraniční poruchou osobnosti americkou psycholožkou Marshou M. Linehan. Diagnózu hraniční poruchy osobnosti chápe DBT stejně, jako ji definuje Diagnostický a statistický manuál Americké psychiatrické společnosti ve své 4. revizi, kritéria ale sestavuje do logických celků, odpovídajících biosociální teorii hraniční poruchy. Významným filozofickým východiskem DBT je dialektika a také zen buddhismus. Významně je DBT ovlivněna kognitivně behaviorální terapií (KBT). DBT se skládá ze čtyř základních modulů – individuální terapie, skupinový nácvik dovedností, telefonický **koučink** a konzultační tým. DBT prokázala svoji účinnost v několika randomizovaných kontrolovaných studiích, a to zejména u žen s hraniční poruchou, které vykazují sebepoškozování a sebevražedné myšlenky.

Klíčová slova: DBT, biosociální teorie, hraniční porucha osobnosti, všímavost, regulace emocí

SUMMARY

Dialectical behavior therapy (DBT) has been formed by American psychologist Marsha M. Linehan for patients with Borderline personality disorder (BPD). The diagnosis of Borderline personality disorder is understood in DBT in the same way as in Diagnostic and Statistical Manual, forth revision (DSM-IV) of the American Psychiatric Association. However, DBT rearranges the BPD criteria into logical units corresponding to the biosocial theory of BPD. An important philosophical background of DBT is dialectics as well as Zen Buddhism. Further, DBT has been significantly influenced by cognitive behavioral therapy (CBT). DBT consists of four basic modules – individual therapy, skills training group, telephone coaching and consultation team. DBT has shown its effectivity in several randomized controlled studies, mainly in women with BPD who self-harm and have suicidal ideation.

Key words: DBT, biosocial theory, borderline personality disorder, mindfulness, emotion regulation

1. HISTORIE DIALEKTICKÉ BEHAVIORÁLNÍ TERAPIE

Dialektická behaviorální terapie (DBT) je spojena se jménem americké psycholožky Marshy M. Linehan (vyslov Lajnehen) (*1943), profesorky psychologie, psychiatrie a behaviorálních věd na University of

Washington. Jejím původním výzkumným zájmem bylo vytvořit a vědecky vyhodnotit léčebný program pro klienty s vysokým rizikem sebevraždy a různými závažnými psychiatrickými poruchami, program, který by vycházel ze zásad medicíny založené na důkazech (*evidence-based medicine – EBM*; Linehan, 1993). Právě téma jejího výzkumu, prevence sebevraždy, ji přivedla ke klientkám s hraniční poruchou osobnosti (*borderline personality disorder;* HPO), avšak sama Marsha Linehan prošla i bolestivou osobní zkušeností v dospívání a mladé dospělosti, kdy vykazovala těžké příznaky hraniční poruchy, jak o tom píše v článku pro New York Times (2011). Roky své výzkumné i praktické práce shrnula v knize *Cognitive-Behavioral Treatment of Borderline Personality Disorder* (Linehan, 1993), v jejímž názvu se paradoxně název DBT vůbec neobjevil, přestože je tato kniha pokládána za „bibli DBT" a i dnes představuje základní studijní materiál pro všechny, kteří se chtějí s DBT seznámit. Kognitivně behaviorální terapie (KBT) v názvu knihy odkazuje na autorčin původní psychoterapeutický směr. Po letech výzkumu ale Linehanová konstatovala, že standardní KBT programy nevedou u klientek s HPO k dostatečnému klinickému zlepšení. Právě napětí mezi přijetím klienta takového, jaký je, a změnou, kterou musí nutně projít, vyžadovalo zařazení technik, které vycházejí z východních filozofií, hlavně ze zenového buddhismu. Jako vyvážení „černobílého" uvažování či přemýšlení v extrémech u klientů s HPO hledala Linehanová filozofické východisko, které našla v dialektické filozofii a na začátku 80. let začala aplikovat v léčbě klientek s HPO dialektický přístup. KBT zase podstatnou mírou přispěla k vytváření strategií k dosažení změny, jako jsou například učení se novým způsobům jednání nebo expoziční techniky (Linehan, 1993). DBT tak bývá řazena do třetí vlny KBT (Šlepecký, 2018).

2. HRANIČNÍ PORUCHA OSOBNOSTI Z POHLEDU DBT

2.1. Diagnostika hraniční poruchy osobnosti

Na rozdíl od mnoha jiných psychoterapeutických škol vychází DBT při definici hraniční poruchy osobnosti (HPO) přísně ze čtvrté verze Diagnostického a statistického manuálu (DSM-IV) Americké psychiatrické společnosti (Tab. 1). Diagnostická kritéria uvedená v manuálu však reorganizuje do podoby, která pokládá za základní problém narušenou regulaci emocí, a vysvětluje tak HPO jako pervazivní poruchu regulace emocí, která se následně promítá do dalších oblastí života klientů. Takto reorganizovaná kritéria jsou pak v terapii také vysvětlována klientům. Reorganizovaná podoba obsahuje všech 9 kritérií DSM-IV, ale logicky přerozdělených do pěti skupin – dysregulace emocí, dysregulace self, dysregulace mezilidských vztahů, dysregulace chování a dysregulace kognicí. Diagnóza HPO je tedy stejná, jak ji chápou lékaři – psychiatři. To umožňuje snazší přenositelnost výzkumu do lékařské praxe. V poslední verzi DSM-5 platné v současné době se kritéria prakticky nezměnila (American Psychiatric Association, 2013). Naopak budoucí verze MKN-11 předpokládá významnou změnu v diagnostice poruch osobnosti a ruší dosud používané specifické poruchy osobnosti (WHO, 2018).

Tabulka 1
Kritéria DSM-IV pro hraniční poruchu osobnosti a reorganizovaná kritéria dle DBT

DSM-IV (DSM 5) kritéria pro hraniční poruchu osobnosti	Reorganizovaná kritéria pro hraniční poruchu osobnosti podle DBT
	Dysregulace emocí
1. Excesivní snahy vyhnout se reálnému nebo domnělému opuštění	Afektivní nestabilita spojená s výraznou reaktivitou nálady (krit. 6)
2. Vzorec nestabilních a intenzivních vztahů	Intenzivní vztek a potíže kontrolovat vztek (krit. 8)
3. Narušení identity, nestabilní sebeobraz	**Dysregulace self**
4. Impulzivita alespoň ve dvou oblastech zahrnujících potenciálně nebezpečné chování (mimo sebepoškozování)	Narušení identity, nestabilní sebeobraz (krit. 3)
5. Sebepoškozování a opakované sebevražedné chování nebo výhružky	Chronické pocity prázdnoty (krit. 7)
6. Afektivní nestabilita spojená s výraznou reaktivitou nálady	**Dysregulace vztahů**
7. Chronické pocity prázdnoty	Excesivní snahy vyhnout se reálnému nebo domnělému opuštění (krit. 1)
8. Intenzivní vztek a potíže kontrolovat vztek	Vzorec nestabilních a intenzivních vztahů (krit. 2)
9. Přechodné stavy paranoidního myšlení nebo disociativní symptomy	**Dysregulace chování**
	Impulzivita alespoň ve dvou oblastech zahrnujících potenciálně nebezpečné chování (mimo sebepoškozování) (krit. 4)
	Sebepoškozování a opakované sebevražedné chování nebo výhružky (krit. 5)
	Dysregulace kognicí
	Přechodné stavy paranoidního myšlení nebo disociativní symptomy (krit. 9)

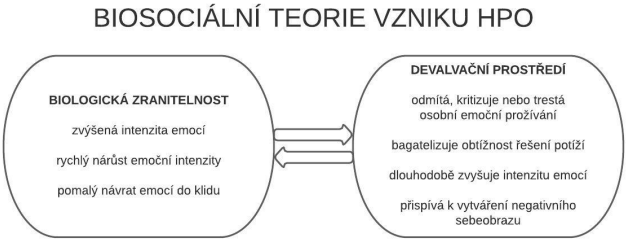
2.2. Hraniční porucha osobnosti jako pervazivní porucha regulace emocí

DBT tedy nahlíží na HPO jako na pervazivní poruchu regulace emocí. V jádru poruchy jsou neobvykle intenzivní emoce a narušená schopnost emoce regulovat. Pro jedince, jejichž emoce se neustále mění, je pak obtížné vytvořit si stabilní sebeobraz (dysregulace self). Vztahy klientů komplikuje obtížná předvídatelnost jejich emočních reakcí a často nepřiměřeně intenzivní emoční reakce. Pokud už klienti mají stabilní vztah, v kontextu nestability self a obtížnosti vztahy udržet je rovněž pochopitelný strach z opuštění blízkými lidmi, kteří klienti často zažívají, a snaha se opuštění vyhnout (dysregulace vztahů). Impulzivní chování je přirozené pro všechny lidi pod vlivem velmi intenzivních emocí. U klientů s HPO vzniká problém v tom, že extrémně intenzivní emoce zažívají na denní bázi, a s tím se pojí právě i zvýšená impulzivita, která je zároveň snahou emoce regulovat (dysregulace chování). Klienti s HPO netrpí poruchami kognitivních funkcí jako takovými, ale vyskytují se u nich kognitivní narušení v emočně intenzivních situacích (Linhartová et al., 2020) and a comprehensive evaluation of impulsivity dimensions is lacking in the litera-

ture. Moreover, it is unclear whether BPD patients manifest impaired cognitive functioning that might be associated with impulsivity in another patient group, such as ADHD, a frequent comorbidity of BPD. Methods We tested 39 patients with BPD without major psychiatric comorbidities and ADHD, 25 patients with ADHD, and 55 healthy controls (HC. Nejčastěji můžeme u klientů pozorovat disociativní stavy, které vznikají jako obranný mechanismus při zahlcení emocemi (typicky depersonalizace, derealizace). Dalším typem kognitivního narušení je paranoidní nastavení, které při extrémně intenzivních emocích vzniká, protože náš mozek má tendenci při zahlcení zúžit pozornost na důležité podněty, což jsou typicky možné hrozby a nebezpečí. Zvýšené vnímání negativních úmyslů druhých lidí a ohrožení pak v tomto kontextu znamená právě zvýšenou ostražitost až paranoidní prožitky (dysregulace kognicí). Příznaky HPO jsou tak v DBT vysvětlovány jako důsledky narušené regulace emocí (Linehan, 1993) a již z tohoto pohledu je zřejmé, že pokud se klienti naučí lépe regulovat své emoce, zmírní se i ostatní příznaky HPO.

2.3. Pohled DBT na sebepoškozování u klientů s hraniční poruchou osobnosti

Sebepoškozování a sebevražedné jednání je z pohledu DBT chápáno jako maladaptivní způsob regulace emocí nebo řešení problémů (Linehan, 1993). Klienti s HPO mají zvýšený práh bolesti (Bohus et al., 2000) a zároveň bolest u nich na rozdíl od zdravých lidí způsobuje snížení intenzity emocí a snížení aktivity amygdaly (Schmahl et al., 2006). Klienti se pak typicky sebepoškozují v situacích, kdy zažívají bolestivé emoce, a primární motivací k sebepoškozování je obvykle úleva od emoční bolesti. Sebepoškozování však neřeší příčiny, které k bolestivé emoci vedly, a zároveň má řadu negativních důsledků, se kterými se klienti následně potýkají. Můžeme hovořit o bludném kruhu sebepoškozování (Obr. 1).



Obr. 1

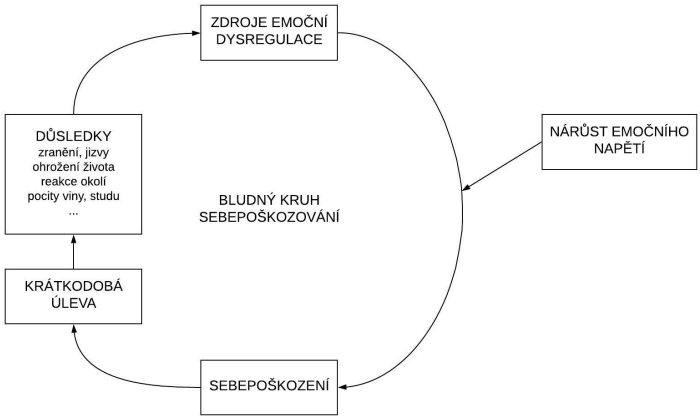
Nestabilní afektivita a porucha regulace emocí vede opakovaně k emocím takové intenzity, kterou je potřeba regulovat. Klienti však zároveň nemají vytvořeny adaptivní způsoby regulace emocí. Často se brzy naučí, že bolest vede ke chvilkovému zmírnění emocí, a když zažívají bolestivé emoce, začnou se sebepoškozovat. Po sebepoškození přichází úleva, která je primární motivací pro sebepoškozování. Úleva je však pouze chvilková a z dlouhodobého hlediska přináší sebepoškozování řadu negativních důsledků: zdravotní komplikace a ohrožení života, jizvy a potřebu je zakrývat, negativní reakce okolí a především prohlubování vlastních pocitů viny, studu či selhání. Tyto důsledky pak vytvářejí nové krizové situace, které vytvářejí nutkání k sebepoškození. DBT považuje sebepoškozování za život ohrožující chování a terapeuti od klientů vyžadují závazek, že se budou ze všech sil

snažit učit se řešit své potíže jinými způsoby než sebepoškozováním. DBT zároveň vede ke snížení redukce aktivity amygdaly při bolesti u klientů s HPO (Niedtfeld et al., 2017).

2.4. Biosociální teorie vzniku hraniční poruchy osobnosti

DBT je pevně zakotvena v teorii nazývané biosociální teorie osobnosti (Linehan, 1993). Ta předpokládá, že hraniční porucha osobnosti vzniká kombinací vlivů biologických a vlivů prostředí, konkrétně vlivem vrozené biologické emoční zranitelnosti a devalvačního prostředí (Obr. 2). Primární poruchou je narušená emoční regulace, která je biologická v podobě vrozené zvýšené emoční zranitelnosti. Emoční zranitelnost se projevuje tak, že lidé s HPO emočně reagují na slabší podněty, než je to u lidí běžné, jejich emoce narůstají do vyšší intenzity a pomaleji se navracejí do klidového stavu. To samo o sobě nemusí vést ke vzniku psychopatologie, avšak jedná se o rizikový faktor, pokud takový jedinec vyrůstá v devalvačním prostředí (*invalidating environment)*. Devalvace (nebo znehodnocování, angl. *invalidation*) jsou reakce okolí, které potlačují, odmítají, kritizují nebo trestají osobní emoční prožívání jedince. Především negativní emoce bývají odmítány. Takové prostředí předpokládá, že každý člověk dokáže či musí dokázat své emoce regulovat a bagatelizuje obtížnost řešení potíží. Takové prostředí vysoce hodnotí a vyžaduje, aby jeho členové byli šťastní, případně se tak tvářili a celkově měli „pozitivní přístup k životu". Koncept znehodnocujícího prostředí je podobný konceptu vyjadřovaných emocí („expressed emotions") známého z výzkumů rodin klientů se schizofrenií nebo depresivní poruchou (Leff a Vaughn, 1985), kde takové prostředí zvyšuje u klientů míru relapsů těchto duševních poruch.

Prostředí, ve kterém dochází k systematické devalvaci emočních projevů, má pro biologicky zranitelného jedince řadu negativních důsledků. Okamžitými důsledky jsou obvykle frustrace, vztek, zklamání a nejistota a dále zvýšení intenzity prožívaných emocí. Důležitou roli rovněž hraje posilování extrémních emočních reakcí tím, že komunikace nepohody a obtíží na nižší úrovni intenzity je často v devalvujícím prostředí ignorována. Dalším dlouhodobým důsledkem devalvačního prostředí je vznik negativního sebeobrazu, kdy jedinec systematicky dostává zprávu, že je s ním něco v nepořádku. A dalším důsledkem je, že jedinec vyrůstající v devalvujícím prostředí se obvykle naučí sám sebe a své emoce de-



Obr. 2 – **Bludný kruh sebepoškozování**

valvovat (neuznávat jejich oprávněnost) a potlačovat (sebedevalvace).

Vrozená snížená schopnost emoční regulace a devalvační prostředí na sebe působí transakčně. To znamená, že původně nízká závažnost emoční dysregulace a jen mírně devalvující prostředí se vzájemným působením vyvíjejí v silně vyjádřené formy obojího. Není obtížné si představit, že projevy dítěte se sníženou schopností regulace emocí jsou pro rodinu velmi zátěžové. Devalvace (neuznávání oprávněnosti) emočních projevů dítěte nebo nepřiměřený důraz na jejich regulaci na základě přesvědčení, že je to snadné, však vede u dítěte k ještě silnější emoční odpovědi, což zase posílí devalvační chování rodiny vůči němu. Emoce dítěte tak postupně narůstají do extrémních hodnot, aby na ně okolí vůbec zareagovalo adekvátním způsobem.

2.5. Dialektická dilemata u klientů s hraniční poruchou

Linehanová (1993) aplikuje dialektiku jako určitý pohled na život a popisuje její tři základní charakteristiky. Tou první je princip vzájemné souvislosti a celistvosti. Je to holistický přístup, kdy zkoumání součástí systému má smysl jen tehdy, když se zkoumají tyto součásti ve vztahu k celku. Jedna věc nemůže existovat bez druhé, ze vztahu k ní získává své vlastnosti a tento vztah se vyvíjí a mění. Druhou charakteristikou je princip polarity. Realita není statická, ale sestává ze vzájemně protikladných sil (teze a antiteze) a jejich spojení (synteze) ihned vytváří další tezi a antitezi. Tedy i u jedinců s HPO je v každé jejich dysfunkci něco funkčního a v každém destruktivním projevu je obsaženo něco konstruktivního. Tento princip vedl Linehanovou ke konstatování, že moudrost vzniká v protichůdnostech. Výrazně to posílilo roli validizace v DBT, neboť každé dysfunkční chování je v určitém ohledu i funkční a jeho funkci není třeba odvozovat z minulosti, ale lze ji hledat v přítomnosti. V praxi pak často stačí upravit výroky obsahující spojku „(a)nebo" na spojku „a" (např. proti „Buď mě miluje, anebo je na mě naštvaný" stojí dialektický výrok „Miluje mě a je na mě naštvaný"). Stejný princip vedl k vytvoření konceptu „moudré mysli". Potenciál pro změnu k lepšímu je již obsažen v současném, byť klinicky závažném stavu, a „moudrá mysl" jej dokáže rozpoznat a využít. Poslední charakteristikou je princip neustálé změny. Napětí mezi tezí a antitezí vede v každém systému ke změně. Stav systému po změně

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ovšem ihned obsahuje další tezi a antitezi, což způsobuje, že změna je nepřetržitá. Změna je tak jedinou konstantou života. Pravda není ani absolutní, ani relativní, ale neustále se mění a má mnoho perspektiv, z nichž ji můžeme pozorovat.

Z pohledu dialektiky je možno na projevy HPO nahlížet jako na dialektické selhání. „Splitting" čili „štěpení", což je významný pojem v psychoanalytickém chápání hraniční poruchy (Kernberg, 1984), lze dialekticky chápat jako „zaseknutí se" buď v určité tezi, nebo určité antitezi a neschopnost pokročit k jejich syntéze. I na projevy zjevného chování klientů s HPO lze nahlížet z dialektické perspektivy. Linehanová (1993) popisuje tři základní dialektická dilemata platná pro vzorce chování hraničních klientů. Jsou to 1. emoční zranitelnost versus sebedevalvace, 2. aktivní pasivita versus zdánlivá kompetence a 3. nepolevující krize versus potlačené truchlení.

První dilema se u klientů projevuje tím, že střídají stav, kdy validizují svoji zranitelnost a současně obviňují druhé lidi, osud a zákony světa a věří tomu, že to, co se jim děje, je nespravedlivé a nemělo by se dít. Na druhé straně je pak stav, kdy vše špatné, co se jim děje, přisuzují tomu, že jsou sami špatní. Takovou míru sebedevalvace až nenávisti k sobě samému stěží najdeme u jiných klientů. Velmi často také klienti s hraniční poruchou nadhodnocují snadnost, s jakou se dá dosáhnout změny chování nebo emocí. Pro terapeuta toto dilema znamená, že musí v léčbě pečlivě dialekticky balancovat mezi přijetím klienta takového, jaký je, a navozením změny. Terapie, která by klienty pouze přijímala, by pro ně byla devalvační, protože klienti jasně formulují svůj život jako utrpení a v terapii hledají změnu. Naopak terapie zaměřená jen na změnu by je utvrzovala v tom, že jsou špatní.

Druhé dilema zdánlivé kompetence a aktivní pasivity znamená u klienta to, že někdy nedůvěřuje vlastním prožitkům a není si jistý, jak se chovat, a potřebuje pomoc. Protože však podle přesvědčení klienta není závislost druhými lidmi kladně hodnocena, snaží se, především v období pozitivních emočních stavů, vystupovat nezávisle a kompetentně. Mnozí klienti také ve svém životě skutečně kompetentní bývají. Pro terapeuta to znamená, že si musí dávat pozor na to, aby nepřeceňoval schopnosti, které klient prezentuje, a zároveň nepodceňoval schopnosti, které klient skutečně má.

Třetí dilema mezi nepolevujícími krizemi a potlačeným truchlením znamená, že klienti nadměrně potlačují truchlení, což krátkodobě vede ke snížení emoční bolesti, ale zároveň to snižuje míru podpory z okolí. Chování typické pro potlačené truchlení je často chování impulzivní – sebepoškozování, nadměrné užívání alkoholu, riskantní jízda automobilem, přehnané utrácení peněz a riskantní sexuální aktivity. Takové chování ovšem vytváří další krize. Pro terapeuta to znamená, že se někdy s klientem setkává ve stavu krize, pod obrazem silného a vše ostatní překrývajícího afektu, a jindy se naopak klient jeví, jako by emočně vůbec nereagoval. Cílem terapeuta je klientovi pomoci, aby těmto emočním stavům porozuměl a také mu nabídnout naději, že dokáže proces truchlení přežít. To vyžaduje, aby terapeut klienta učil způsobům bezpečného truchlení.

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3. ZÁKLADNÍ TERAPEUTICKÉ STRATEGIE V DBT

3.1. Dialektika a fenomenologická empatie

DBT terapeuti zaujímají v souladu s dialektickou filosofií základní postoj, že neexistuje žádná absolutní pravda a že pokud se objeví rozpory, cílem je hledat jejich syntézu spíše než odpověď na otázku, kdo má pravdu. Dialektická filosofie nezakazuje mít svůj vlastní názor a nepovažuje rozpory v názorech za nežádoucí, poukazuje pouze na dialektický způsob řešení rozporů, který snižuje napětí ve vztazích a zvyšuje flexibilitu a schopnost řešení obtíží. Terapeuti se také drží zásady, že chování klientů nekritizují a nehodnotí, ale naopak hledají nepejorativní a fenomenologicky empatické interpretace jejich chování. DBT předpokládá respekt vůči klientům a vychází z předpokladu, že klienti (stejně jako všichni lidé) dělají maximum možného v dané chvíli a zároveň se chtějí zlepšovat (Linehan, 1993). Terapeuti zaujímají dialektický a fenomenologický přístup nejen vůči klientům, ale i vůči sobě a ostatním terapeutům. Na dialektiku je tak v DBT nahlíženo jako na dovednost a zároveň jako na způsob přemýšlení o světě, který je DBT terapeutům vlastní i mimo terapeutickou práci.

Dialektický přístup se prolíná veškerým kontaktem s klienty. Kdykoliv klient přemýšlí v extrémech nebo zvažuje pouze jednu stranu určitého problému, ptáme se: Co klient přehlíží? Dá se na danou situaci podívat z jiného úhlu pohledu? Pomáháme klientům vidět, že každé jejich chování může dávat z určitého úhlu pohledu dávat smysl. V reakci na extrémní a černobílé myšlení typu „můžu jednat buď jen takto, nebo jen přesně naopak“, učíme klienty vnímat škálu různých možných způsobů chování a řešení problémů, čímž roste flexibilita klientů reagovat dovedně v různých životních situacích a reagovat na změny. Klienti se dále učí, jak v životě hledat rovnováhu mezi různými protiklady (např. pracovat a odpočívat, věřit lidem a být ostražitý, být samostatný a říct si o pomoc apod.) a že zdánlivé rozpory mohou být oba pravdivé (např. můžu mít s někým neshody A ZÁROVEŇ můžeme být přátelé, dělám maximum možného v současné chvíli A ZÁROVEŇ se potřebuji zlepšit, můžu být

sám sebou A ZÁROVEŇ být v kontaktu s druhými lidmi apod.). Dialektika nás dále učí, že jsme všichni propojeni a že změna je v životě jediná konstanta. To znamená, že se klienti učí vnímat dopady svého chování na ostatní lidi a dopady vlivu okolí na ně samotné (namísto vnímání vlastního chování a chování druhých jako nesouvisejících izolovaných jednotek), přijímat změny jako nevyhnutelnou součást života a trénovat reagování na změny. Dialektika se projevuje také ve vyvažování terapeutických strategií, přístupů a technik. Zásadní je pak v terapii vyvažování postoje přijetí a úsilí o změny. Přijmout je zapotřebí zejména fakta, bolest či emoce, naopak je třeba usilovat o změnu nefunkčních přesvědčení, nepřiměřené intenzity emocí a neužitečného chování.

3.2. Nástroje přijetí a změny v DBT

Základní technikou přijetí v DBT je validizace, tedy uznání platnosti a oprávněnosti. Validizace znamená, že respektujeme klienta takového, jaký je, věnujeme mu pozornost, snažíme se porozumět jeho úhlu pohledu a poukazujeme na to, co je funkční i v nefunkčním a sebedestruktivním chování. Validizace je v DBT základním terapeutickým nástrojem a sama o sobě je léčivá vzhledem k historii devalvace u klientů s hraniční poruchou osobnosti. Jako platné přitom uznáváme pouze to, co platné je – fakta, minulost, bolest, emoce, různost názorů. Validizace naopak neznamená podporovat, co je neplatné a neoprávněné. Zatímco emoce jsou platné vždy, chování již být oprávněné nemusí. Dialektickou reakcí v tomto smyslu je například: „chápu, že máš vztek, a zároveň nesouhlasím s tím, že se chováš agresivně“. Validizace tak neznamená souhlas nebo schvalování („chápu, že tuhle situaci vidíš jinak než já, a zároveň já mám na to odlišný názor“). Validizace také neznamená říkat klientům jen pozitivní věci. Validizace je zároveň dovednost, kterou aktivně učíme používat také klienty jak ve vztahu k druhým lidem, tak ve vztahu k sobě (sebevalidizace).

DBT dále rozlišuje čtyři základní typy nástrojů k dosahování změny v terapii. Těmi jsou analýza a modifikace důsledků chování, kognitivní modifikace, expoziční techniky a trénink dovedností (Linehan, 1993). Analýza a modifikace důsledků chování zahrnuje mapování faktorů, které posilují škodlivé chování a které potlačují potenciálně vhodnější chování, a úpravu těchto faktorů. Trénink dovedností pak probíhá ve skupině, kde se klienti učí novým dovednostem, a ty se následně učí používat ve svém každodenním životě.

4. TERAPEUTICKÉ FUNKCE A MODULY DBT

4.1. Pět základní funkcí DBT

Komplexní DBT terapie zahrnuje čtyři základní součásti a plní pět základních funkcí. Zatímco některé terapie mohou využívat prvky DBT, komplexní DBT program zahrnuje všechny základní součásti a je zapotřebí u klientů s nejzávažnějšími problémy. Pět základních funkcí, které DBT plní, jsou 1. motivace klientů, která je primárně posilována v individuální terapii, 2. trénink nových dovedností, který se provádí ve skupině, 3. přenesení nových dovedností do běžného života, které je rozvíjeno pomocí telefonického koučinku, 4. motivace terapeutů, která je rozvíjena pomocí konzultačního týmu, a 5. stanovení jasné struktury, která je dosahována strukturou samotné terapie, zakotvením

terapie v teorii či nástroji sebesledování klientů. Čtyři základní součásti DBT jsou individuální terapie, trénink dovedností ve skupině, telefonický koučink a konzultační tým terapeutů. Nedílnou součástí terapie je pak přípravná fáze (angl. *pretreatment*), kterou absolvují všichni klienti před vstupem do terapie.

4.2. Stanovení struktury

Samotná terapie je jasně strukturována jak kolem jejích jednotlivých součástí, tak kolem teorie. Dbá se na dodržování pravidel, závazků pravidelné účasti a včasných příchodů na terapeutická sezení. Zásadním prvkem je pak zdokonalování schopnosti klienta monitorovat své vlastní psychické procesy (jinými slovy, zvyšování sebeuvědomování). Základním nástrojem v této oblasti je deníková karta (Obr. 3). Deníková karta je nástroj, kde si klienti po celou dobu terapie každý den zaznamenávají základní informace o svém prožívání a chování v každém dni. Sledují v ní výskyt chování ohrožujících život a nutkání k těmto chováním, užívání medikace, drog a alkoholu, intenzitu emocí nebo také nutkání ukončit terapii. Dále je v deníkové kartě sledováno používání dovedností. S deníkovou kartou (obr. 3a, 3b) pracujeme primárně v individuální terapii (viz níže).

4.3. Přípravná fáze terapie

Před samotným zahájením DBT programu klienti procházejí tzv. přípravnou fází (Linehan, 1993). Jedná se obvykle o čtyři až pět individuálních sezení, ve kterých ověřujeme diagnózu hraniční poruchy osobnosti a klient je seznámen s pojetím hraniční poruchy v DBT, biosociální teorií, metodami dialektiky i behaviorálními metodami, s průběhem DBT a jejími jednotlivými součástmi. Po celou dobu je klient motivován k terapii a teorie DBT je vztahována k individuálnímu prožívání klienta. V závěru přípravné fáze pak klient podepisuje závazky, se kterými do DBT vstupuje, přičemž minimálním závazkem je snažit se ze všech sil pracovat na svých potížích způsoby, které nezahrnují sebepoškozování a sebevražedné jednání, a účastnit se všech součástí terapie. Klient tak vstupuje do DBT informován o terapii, motivován propojením teorie a jeho vlastních zkušeností a s konkrétními závazky. U závažně sebevražedných klientů v přípravné fázi rovněž vypracujeme individuální antisuicidální plán, tedy sled opatření, která budou uplatněna, pokud bude klient cítit silné nutkání k sebevraždě, nebo pokud se o sebevražedném plánu dozví terapeut.

4.4. Trénink dovedností ve skupině

Na rozdíl od jiných psychoterapeutických přístupů slouží skupina v DBT k učení a nácviku potřebných dovedností. Mnoho druhů dysfunkčního chování u hraničních klientů vyplývá z nedostatku dovedností. Na výuku dovedností se proto v DBT klade velký důraz. Skupinoví terapeuti, kteří jsou vždy dva, jsou tedy učitelé a trenéři. Skupina má předem danou strukturu i téma. Začíná se vždy krátkým cvičením všímavosti. Následuje kontrola úkolů z minulé skupiny. Po kontrole úkolů se přechází k výuce nových dovedností, které pak mají klienti za úkol trénovat do příští skupiny. Během tréninku se využívá řada pracovních materiálů (Linehan, 2014).

V obvykle půlročním cyklu se probírají 4 tematické okruhy dovedností (Linehan, 2014): všímavost (*mindfulness*), tolerance

DBT deníková karta	Jméno:	Kolikrát za týden vyplněno? ☐ denně ☐ 4x-6x ☐ 2x-3x ☐ 1x	Vyplněno v sezení? ANO x NE	Vyplňováno od – do:

	Největší nutkání v daném dni:			Nejvyšší hodnocení v daném dni:			Medikace / Drogy:								Chování:			Emoce:		Další:	
	zabít se	sebe-pošk.	drogy	emoční bolest	fyzická bolest	radost	alkohol		drogy		medikace dle předpisu	jiná medikace			sebe-pošk.	lhaní	dovednosti*				
	0-5	0-5	0-5	0-5	0-5	0-5	#	co?	#	co?	A x N	#	co?		A x N	#	0-7				
Po																					
Út																					
St																					
Čt																					
Pá																					
So																					
Ne																					

Změny v medikaci tento týden:	* hodnocení dovedností 0 = neupoužil/a jsem a nezvažoval/a jsem to 1 = zvažoval/a jsem to, ale nepoužila, nechtěl/a jsem 2 = zvažoval/a jsem to, ale nepoužil/a, i když jsem chtěl/a 3 = zkoušel/a jsem, ale nešlo to 4 = zkoušel/a jsem, šlo to, ale nepomohly 5 = zkoušel/a jsem, šlo o, pomohly 6 = automaticky jsem je použil/a, nepomohly 7 = automaticky jsem je použil/a, pomohly
Domácí úkoly a výsledky:	
Na jaké dovednosti jste se zaměřili tento týden:	Před sezením:
Poznámky:	Nutkání (0-5): / Přesvědčení, že můžu změnit nebo regulovat moje (0-5):
	ukončit terapii / emoce
	zabít se / myšlenky
	chování

Obr. 3a – **Deníková karta (česká verze Psychiatrické kliniky FN Brno)**

Modul	Vyplněno: ☐ denně ☐ 4x-6x ☐ 2x-3x ☐ 1x ☐ ve skupině		Zakroužkujte dny, když jste procvičovali						
Všímavost		Moudrá mysl	Po	Út	St	Čt	Pá	So	Ne
		CO dělat všímavě: Pozorování	Po	Út	St	Čt	Pá	So	Ne
		CO dělat všímavě: Popisování	Po	Út	St	Čt	Pá	So	Ne
		CO dělat všímavě: Participace	Po	Út	St	Čt	Pá	So	Ne
		JAK to dělat všímavě: Bez hodnocení	Po	Út	St	Čt	Pá	So	Ne
		JAK to dělat všímavě: Jedna věc po druhé	Po	Út	St	Čt	Pá	So	Ne
		JAK to dělat všímavě: Efektivně	Po	Út	St	Čt	Pá	So	Ne
Emoční regulace		Ověřování faktů	Po	Út	St	Čt	Pá	So	Ne
		Opačné jednání	Po	Út	St	Čt	Pá	So	Ne
		Řešení problémů	Po	Út	St	Čt	Pá	So	Ne
		Akumulace pozitivních emocí	Po	Út	St	Čt	Pá	So	Ne
		Snižování emoční zranitelnosti pomocí péče o tělo	Po	Út	St	Čt	Pá	So	Ne
		Všímavost aktuálních emocí	Po	Út	St	Čt	Pá	So	Ne
Tolerance stresu	Zvládání krizových situací	dovednost STOP	Po	Út	St	Čt	Pá	So	Ne
		dovednosti SIPS	Po	Út	St	Čt	Pá	So	Ne
	Přijetí reality	Radikální přijetí	Po	Út	St	Čt	Pá	So	Ne
		Nepatrný úsměv, přijímající ruce, otevřenost	Po	Út	St	Čt	Pá	So	Ne
		Všímavost aktuálních myšlenek	Po	Út	St	Čt	Pá	So	Ne
Efektivita v mezilidských vztazích		„DEAR“	Po	Út	St	Čt	Pá	So	Ne
		„MAN“	Po	Út	St	Čt	Pá	So	Ne
		„GIVE“	Po	Út	St	Čt	Pá	So	Ne
		„FAST“	Po	Út	St	Čt	Pá	So	Ne
		Dialektika v sociálních situacích	Po	Út	St	Čt	Pá	So	Ne
		Potvrzování sebe i druhých	Po	Út	St	Čt	Pá	So	Ne

Obr. 3b – **Deníková karta pokrač. (česká verze Psychiatrické kliniky FN Brno)**

nepříjemných emocí (*distress tolerance*), emoční regulace (*emotion regulation*) a efektivita v mezilidských vztazích (*interpersonal effectiveness*). Všímavost je soubor dovedností, jak plně prožívat realitu takovou jaká je, uvědomovat si a popisovat vnitřní i vnější realitu bez hodnocení či odlišování faktů od hodnocení a interpretací. Cílem všímavosti je snížení utrpení a posílení kontroly nad vlastní myslí. Jedná se o základní dovednost, která je nutná pro použití všech ostatních dovedností. Tolerance nepříjemných emocí je soubor dovedností zahrnující dovednosti pro zvládání krizových situací a dovednosti pro přijetí reality. Dovednosti pro zvládání krizových situací fungují velmi rychle a jsou určeny jen a pouze pro krizové situace – krátkodobé situace, spojené s extrémními emocemi, v nichž typicky hrozí impulzivní a často sebedestruktivní jednání. Cílem je krizi „přežít" a zabránit impulzivnímu jednání, nejedná se však o dovednosti, které vedou k řešení problémů. Dovednosti pro přijetí reality jsou pak užitečné zejména v situacích, které nelze změnit. Dovednosti z okruhů emoční regulace a efektivity v mezilidských vztazích vedou k dlouhodobým změnám. V regulaci emocí se klienti učí rozpoznat, zda právě prožívaná emoce nebo její intenzita odpovídají faktorům situace a zda je efektivní podle emoce jednat. Pokud ne, pak se klienti učí regulovat emoci pomocí dovednosti opačného jednání, pokud je emoce efektivní, učí se klienti řešit problém, který emoci vyvolal. Dovednosti efektivity v mezilidských vztazích pak zahrnují dovednosti, jak dosahovat svých cílů v mezilidských situacích a přitom si pokud možno udržet jak vztahy, tak svoji vlastní sebeúctu. Další dovednosti z tohoto okruhu se týkají například navazování vztahů nebo ukončování destruktivních vztahů.

Adéla Látalová

Mgr. Pracuje na Psychiatrické klinice FN Brno a LF MU jako psycholog ve zdravotnictví a odborný pracovník. Od roku 2019 je frekventantkou psychoterapeutického výcviku v Gestalt terapii (Institut Dialog) a v letech 2019–2020 absolvovala intenzivní výcvik v Dialektické behaviorální terapii ve Velké Británii v institutu British Isles DBT Training, který je odnoží tréninkového institutu Marshy Linehanové. V rámci doktorského studia se věnuje pacientům s hraniční poruchou osobnosti, emoční regulaci a neurálním korelátům DBT.

Ve standardním uspořádání je v každém cyklu tréninku dovedností všímavost zařazena třikrát. Každý klient pak začíná skupinu dovednostmi všímavosti a celý cyklus skupin absolvuje dvakrát za sebou. U standardního půlročního běhu skupin to znamená, že účast v terapii trvá jeden rok. Skupiny jsou obvykle polootevřené a noví klienti vstupují do skupiny právě vždy v bloku všímavosti. Tento postup vede k tomu, že se ve skupině nacházejí účastníci, kteří jsou v DBT různě pokročilí a pokročilejší klienti mohou motivovat nové klienty. Základním úkolem skupiny je tedy co nejefektivněji naučit klienty nové dovednosti, skupinová dynamika se ex-

plicitně neřeší, řeší se jen způsoby chování, které by mohly narušit základní smysl skupiny. DBT dovedností v jednotlivých okruzích existuje mnoho (Linehan, 2014) a konkrétní podobu tréninku dovedností při zachování základních pravidel je možné upravit podle potřeb instituce či klientské skupiny.

4.5. Individuální DBT sezení

Na rozdíl od DBT skupin nemá individuální sezení předem stanovené téma, ale má předepsanou strukturu (Linehan, 1993). Jeho délka je stanovena na 60 minut a počítá se s jedním sezením týdně. Pokud je individuální sezení z jakéhokoliv důvodu vynecháno, mělo by být nahrazeno, aby byla dodržena „předepsaná dávka terapie". Na začátku každého sezení si terapeut od klienta vyžádá jeho deníkovou kartu. Na jejím základě se vytváří program sezení. V DBT existuje jasně určená hierarchie témat, která se v sezení probírají. Důvodem je princip, že aby klient mohl z terapie čerpat, musí být v první řadě naživu a v druhé řadě v terapii. Na prvním místě hierarchie jsou tak chování ohrožující život klienta (*life-threatening behaviors*), kam patří zejména sebevražedné jednání, sebepoškozování a nutkání se zabít nebo se sebepoškodit. Zjednodušeně řečeno to jsou všechny druhy chování, které mohou klientovi znemožnit dožít se dalšího sezení. Pokud se takové chování od minulého sezení vyskytlo, je prioritou a v sezení se provádí jeho podrobná behaviorální analýza a analýza řešení zahrnující již naučené dovednosti.

Na druhém místě hierarchie se nachází chování narušující terapii (*therapy-interfering behaviors*). Zde se jedná o všechny druhy chování, které snižují buď klientovu nebo terapeutovu motivaci společně pracovat a která mohou ohrozit setrvání klienta v terapii nebo jeho pokrok v terapii. Konkrétně se může jednat o: vynechávání sezení, pozdní příchody nebo protahování sezení, neplnění úkolů, lhaní, hostilní reakce nebo mlčení, přílišná únava, disociace nebo panika v sezení a podobně (Linehan, 1993). Na tyto způsoby chování pak v DBT nenahlížíme jako na důvody k ukončení terapie, ale na jedny z důvodů, proč klient v terapii je. Spolupráce v terapii je pak v DBT pojímána jednak jako podmínka pro pokrok v terapii a zároveň jako dovednost, kterou je klienty třeba učit. Linehanová (1993) tak zdůrazňuje, že spolupracující chování mnohdy nelze od klientů pasivně očekávat a je třeba jej aktivně učit a rozvíjet. Koncept chování narušujícího terapii je klientům vysvětlován již v přípravné fázi terapie. Klientům sdělujeme, že pokud se taková chování vyskytnou, budeme se jimi vždy zabývat, avšak nikoliv s cílem klienty kritizovat nebo poučovat, ale s cílem najít vhodnější způsoby chování tak, aby měl klient z terapie co největší užitek. Tento přístup výrazně zvyšuje pravděpodobnost, že klienti budou ochotni se tímto chováním zabývat. Jednou z důležitých funkcí DBT je pak i zvyšování schopnosti stabilně docházet do terapie a pracovat na pokroku v terapii, která může být zásadní v navazující terapii klientů.

Třetí v řadě priorit v individuální terapii jsou chování narušující kvalitu života. Jde o nejrůznější problémy od užívání alkoholu a drog, přes rizikové sexuální chování až po hladovění či zvracení nebo jakékoliv další individuální potíže klientů. Agenda sezení je tedy nastavena podle těchto priorit a často se stává, že na témata, které by

chtěl klient probírat, se již nedostane. Tímto způsobem se klient učí o důsledcích svého chování. Zároveň je však vždy na konci sezení vyhrazen určitý časový prostor pro akutní individuální potíže či události, o kterých klient potřebuje mluvit.

4.6. Telefonický koučink

Telefonický koučink je standardní součástí komplexní DBT terapie. Každý klient má možnost zavolat svému individuálnímu terapeutovi v situaci, kdy se snaží využít některou z DBT dovedností a zároveň potřebuji poradit. V takovém hovoru klient nejdříve popíše situaci a sdělí, které techniky zkoušel a s jakým výsledkem. Terapeut pak s klientem hledá další dovednosti a probere konkrétní postup řešení situace. Cílem je přenesení dovedností do běžného života, tedy posilování schopnosti využít dovednost v konkrétní situaci v reálném čase. Telefonát může také sloužit ke sdělení výsledku nějakého úkolu. Pokud klient telefonuje, že je v krizi, že nic nevyzkoušel, popřípadě se chce zabít, může terapeut aktivovat antisuicidální plán. Takové chování je zároveň chápáno jako terapii narušující. Za chování narušující terapii se považuje i takové, kdy by klient měl telefonického kontaktu využít, ale neudělá to. To je v praxi mnohem častější problém než nadužívání telefonického koučinku.

4.7. Konzultační tým

Práce s klienty s hraniční poruchou osobnosti přináší specifické problémy. Pro terapeuty je to často práce náročná, často se potýkají s krizovými situacemi, sebevražedným jednáním nebo malým pokrokem klientů v terapii, někdy se dostávají v terapii do slepé uličky, někdy se objevují vztahové problémy. Konzultační tým představuje intervizní setkání, které probíhá pravidelně každý týden a kterého se účastní všichni členové DBT týmu, kteří přímo pracují s klienty, ať již jako individuální terapeuti nebo terapeuti ve skupinách. Každotýdenní účast na konzultačním týmu je standardní součástí DBT terapie (Linehan, 1993). V rámci konzultačního týmu přinášejí členové týmu své individuální prožívání v terapii s konkrétními klienty (v psychodynamickém pojetí bychom mohli mluvit o práci s protipřenosem terapeuta). Ostatní terapeuti pak využívají svoje DBT dovednosti a podporují terapeuta v dialektickém přemýšlení, pomáhají terapeutovi nacházet nehodnotící interpretace chování klientů, vyvažují podporu a validizaci terapeuta a možnosti řešení problémů v terapii a pomáhají si navzájem sledovat své limity v terapii. Hlavními cíli konzultačního týmu jsou zmírnění negativních interpretací chování klientů, podpora terapeutů a prevence vyhoření terapeutů. Nejedná se tedy primárně o supervizi, ale spíše o jakousi formu DBT práce s a mezi terapeuty samotnými s cílem udržení a zvyšování efektivity a motivace terapeutů.

4.8. Uspořádání DBT programů a jejich využití u jiných typů problémů

DBT byla původně zamýšlena jako ambulantní psychoterapie. Ve standardním uspořádání probíhá nejprve přípravná fáze s frekvencí jednoho sezení týdně a poté jeden rok DBT terapie, během kterého klient dochází 1x týdně na individuální terapii a 1x týdně na skupinový trénink dovedností. Trénink dovedností je organizován do půlročního cyklu a během terapie absolvují klienti dva cykly tréninku dovedností za se-

bou. DBT lze však při zachování základních pravidel modifikovat do podoby, která je šitá na míru konkrétního pracoviště nebo klientské skupiny. Existuje řada ambulantních programů s kratším docházením (např. půl roku) nebo také DBT programy probíhající za hospitalizace, která typicky trvá 12 týdnů. DBT byla zároveň modifikována pro použití u řady dalších problémů, u kterých se objevují specifické poruchy regulace emocí. Konkrétně existují například adaptace zaměřené na léčbu posttraumatické stresové poruchy (DBT-PTSD), poruch příjmu potravy (DBT-ED) nebo na adolescentní (DBT-A) i dětskou klientelu (DBT-C) (Swales, 2018).

5. Účinnost DBT

Účinnost DBT u jedinců s hraniční poruchou osobnosti byla dokumentována v celé řadě klinických studií. Několik meta-analýz potvrzuje, že u jedinců s hraniční poruchou osobnosti vede absolvování DBT programu ke snížení počtu sebevražedných pokusů a také ke snížení četnosti a závažnosti sebepoškozujícího chování (DeCou, Comtois, & Landes, 2019; Stoffers-Winterling et al., 2012). Další studie ukazují, že DBT může u klientů snížit depresi, úzkost a pocit bezmoci (Bohus et al., 2004; Koons et al., 2001). Několik studií také poukazuje na souvislost mezi DBT a redukcí vzteku a impulzivního chování (Koons et al., 2001; Linehan, Tutek, Heard, Heidi, & Armstrong, 1994; Verheul et al., 2003).

Z výsledků dosavadních studií se zdá, že DBT představuje vhodnou formu léčby zejména pro klienty, kteří mají chronické potíže se sebepoškozujícím a sebevražedným chováním. U těchto vysoce rizikových klientů DBT napomáhá dosažení stabilizace a behaviorální kontroly a umožňuje jim navázat další psychoterapeutickou prací (O'Connell & Dowling, 2014; Verheul et al., 2003). Efektivitě DBT u klientů s hraniční poruchou osobnosti se detailněji věnujeme v samostatném článku (Látalová, Linhartová, & Kašpárek, v tisku).

Studie van den Boschové a jejích kolegů (2005) ukazuje, že dosažený efekt může u klientů přetrvat i po skončení DBT programu. Autoři této studie však upozorňují, že pro udržení účinku je důležité, aby klienti v následujících fázích léčby pokračovali v psychoterapeutické práci. Mohou přitom využít navazující DBT (tzv. druhá fáze; Linehan, 1993), avšak DBT klienty připravuje pro efektivní navázání v jakémkoliv jiném typu psychoterapie tím, že zvyšuje dovednost sebeuvědomování klientů, dovednosti samostatného zvládání krizových situací, dovednost samostatné práce mezi terapeutickými sezeními nebo dovednosti strukturace času, dodržování závazků a další.

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Role autorů: Pavel Theiner prováděl rešerši literatury a přispěl svými praktickými zkušenostmi do kapitol 1, 2, 3 a 4, jichž byl spoluautorem. Pavla Linhartová prováděla rešerši literatury a přispěla svými praktickými zkušenostmi do kapitol 1, 2, 3, 5, jichž byla spoluautorkou, a byla hlavní autorkou kapitoly 4. Adéla Látalová prostudovala studie o účinnosti DBT a byla hlavní autorkou kapitoly 5. Všichni autoři se podílejí na výzkumu účinnosti programu DBT

na Psychiatrické klinice FN Brno a LF MU financovaného AZV MZ ČR. Všichni autoři jsou aktivními DBT terapeuty.

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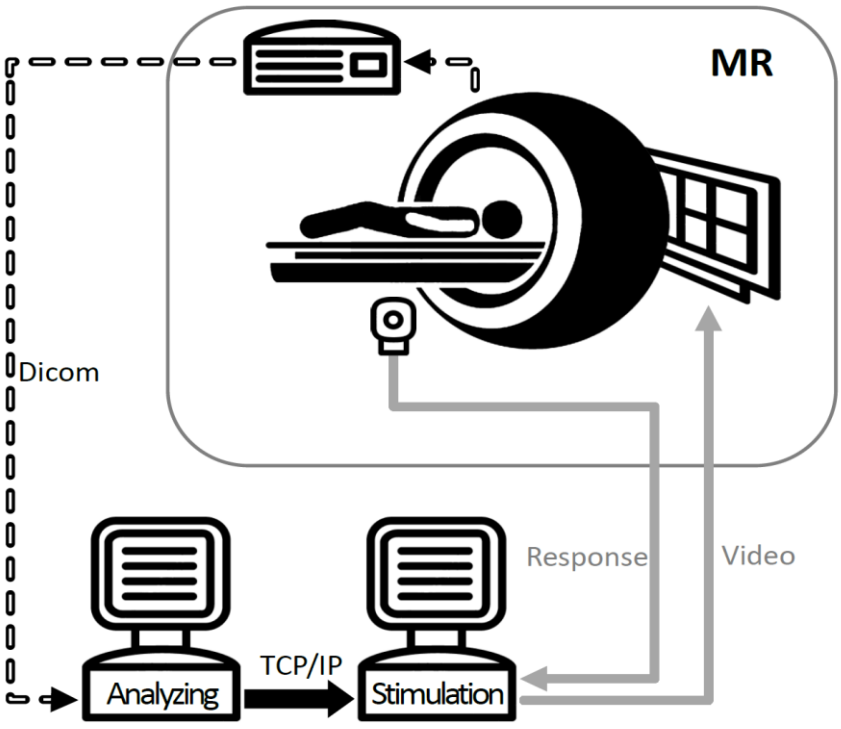
4.2 fMRI neurofeedback

Real-time fMRI neurofeedback (rt-fMRI-NF) is an innovative method which allows participants to learn and train to voluntarily regulate their brain activity (Linhartová, Látalová, et al., 2019, Annex 9). In rt-fMRI-NF studies, the blood-oxygen level dependent (BOLD) signal from a selected brain area is measured and presented back to a subject in the scanner in a visual (or other) form (Fig. 3). With this real-time presentation of their brain activity, the participants learn to influence their current brain activation. The goal of rt-fMRI-NF is to promote the subject's learning self-control over the activity in a selected brain area and, as a result, over the mental state corresponding with the given brain region. The main advantage of fMRI neurofeedback as compared to more known electroencephalography (EEG) neurofeedback is the high special resolution of MRI. This means that we can target any selected brain region or even brain connectivity or brain networks with fMRI neurofeedback, and thus we can target specific brain activity corresponding with a given problem or function. Moreover, we can teach patients to downregulate or upregulate the brain region activity and we can use various forms of design and visual (or other) presentations tailored to specific populations and problems.

Figure 1: Real-time fMRI neurofeedback schema.



First step in designing an rt-fMRI-NF study, is to select the target population, define an impaired function or a current symptom, and identify a brain region (or brain connectivity or

brain network) which is associated with the function or symptom. In the second step, the targeted brain region needs to be localized either anatomically (according to a neuroanatomical atlas), or functionally (e.g., present the participant with noise during fMRI if we want to localize the auditory cortex). In the final step, we need to create a neurofeedback task for training of the impaired function or symptom reduction.

During the task, brain activity has to be presented to the participant. This is typically done by different forms of visual scales, but it can also be done e.g. by changing the brightness of a picture or by a sound indication and other means. For example, one study focused on children with ADHD presented the neural activity as a descending or ascending spaceship which was used to attract the children and keep their motivation (Alegria et al., 2017). Patients then need to be instructed to increase or decrease the signal by upregulating or downregulating their brain activity according to the task goal. Various stimuli can be used to elicit a brain activation which is then supposed to be downregulated (e.g., elicit emotions by emotional pictures (Paret et al., 2014, 2016) or personalized scripts (Gerin et al., 2016) and then train downregulation in patients with emotion regulation problems). Finally, participants can be instructed to use a specific method for training, or they can be instructed to try and find their own method for brain regulation. This can be especially helpful in cases where we actually don't know the exact strategies how to reduce the symptoms (e.g., tinnitus; Emmert et al., 2017) or if we want the participants to try different strategies and find which works the best for them individually.

The common problem in rt-fMRI-NF studies is the selection of a control condition. Especially in cases such as emotion regulation which can be trained outside the scanner, it is important to bring evidence that rt-fMRI-NF really causes an improvement in the training since rt-fMRI-NF is an expensive and demanding method. Three types of control conditions are used in studies (Linhartová, Látalová, et al., 2019). First, the subject is doing the same task in the scanner or outside the scanner with no neurofeedback presentation. Generally, this option is not recommended since the experiment cannot be blinded and there are differences in motivational aspects between the groups (since the participants can enjoy the neurofeedback procedure and find it interesting, or on the other hand, they can become frustrated if the neurofeedback does not correspond with their wishes). Second, sham neurofeedback can be presented, such as a random "neurofeedback signal" or so called "yoked neurofeedback" which is presentation of the neurofeedback signal from the same task, but from a different participant. The biggest objection against this method is that participants can get frustrated by the fact that the neurofeedback does not correspond with what they are doing in the scanner. Third, neurofeedback from a different brain region of the same participant can be presented in the control condition. This method is probably the most methodologically strict and reasonable, however, the problem is which region to select. In general, it should be a region which can be voluntarily regulated in the similar extent as the targeted region and, at the same time, is not connected to the given function or symptom.

4.2.1 fMRI neurofeedback in borderline personality disorder

rt-fMRI-NF studies in patients with BPD are focused on training of emotion. Several types of designs can be used in emotion regulation rt-fMRI-NF studies (Linhartová, Látalová, et al., 2019). First, neurofeedback from a brain region which corresponds with emotional experiencing (typically amygdala or insula) can be presented and patients then learn to either decrease their negative emotional experiencing (typically simultaneously with presentation of stimuli that elicit emotions; e.g. Paret et al., 2016)), or to increase their positive emotional experiencing (typically by contemplating on their positive memories; e.g. Young et al., 2014). Second, neurofeedback from a brain region or brain connectivity which corresponds with the emotion regulation function (typically different parts of prefrontal cortex or limbic-prefrontal connectivity) can be presented and patients then learn to increase their ability of emotion regulation (e.g. Sarkheil et al., 2015). We have published a review of rt-fMRI-NF studies in emotion regulation (Linhartová, Látalová, et al., 2019; Annex 8) which implies that the strongest evidence for the rt-fMRI-NF effectiveness has been shown in increasing positive emotion experiencing in patients with depression, in decreasing anxiety in patients with anxiety disorders, and in decreasing PTSD symptoms in patients with PTSD.

Regarding the rt-fMRI-NF studies in patients with BPD, in a pilot study by Paret et al. (2016) ten patients with BPD underwent four sessions of amygdala downregulation training. The patients were presented with pictures eliciting negative emotion experiencing simultaneously with scale presenting their current amygdala activity. The tasks for the patients were either to passively view the pictures (view condition), or to try to decrease their amygdala activity using the neurofeedback aid (regulate condition). Results showed that amygdala neurofeedback led to successful right amygdala regulation in regulate vs. view condition. Further, task-related amygdala-ventromedial prefrontal cortex connectivity increased during the training session in regulate vs. view condition, and resting state amygdala-lateral prefrontal cortex connectivity increased after the training sessions. Symptomatically, the level of dissociation decreased after the training. In sum, this pilot study showed that patients with BPD can regulate amygdala during viewing negative pictures and that amygdala neurofeedback training also led to brain connectivity associated with emotion regulation increase in patients with BPD.

In their following study (Zaehringer et al., 2019), 24 patients with BPD underwent four session of amygdala downregulation training with the same design as in the previous study (Paret et al., 2016). The main effects were assessed by self-reported emotion regulation problems (Difficulties in Emotion Regulation Scale; DERS; Gratz & Roemer, 2004), by clinical interview measuring the current severity of borderline symptoms (Zanarini rating scale for BPD; ZAN-BPD; Zanarini, 2003), and by ecological momentary assessment measuring positive and negative emotional experiencing and emotion regulation during the day for four consecutive days (assessed 12 times per day by a short questionnaire filled out on the

participants' mobile phone). The results showed that patients were successfully able to downregulate their amygdala activity during the course of the training in regulate vs. view condition. Moreover, self-reported emotion dysregulation and clinician-assessed BPD severity lowered after the neurofeedback training. Regarding ecological momentary assessment, negative affect decreased, and emotion regulation increased after the training. In sum, this study showed that amygdala neurofeedback emotion regulation training led to decrease in emotion dysregulation in everyday life and to decrease in BPD symptoms in patients with BPD.

Although amygdala fMRI neurofeedback shows promising results in several mental disorders including BPD, the high cost and low general availability of MRI machines severely limits the clinical use of this method. Because of that, an electrocortical derivate of deep-brain amygdala activation was developed – the so called amygdala-related electrical fingerprint (amygdala-EFP; Meir-hasson, Keynan, Kinreich, & Jackont, 2016). The amygdala-EFP method allows amygdala neurofeedback training outside of MRI machine, using only three EEG electrodes. The amygdala-EFP has been already shown to be effective in decreasing symptoms of PTSD (Fruchtman-Steinbok et al., 2021; Keynan et al., 2019). The first study of amygdala-EFP in patients with BPD has been published in 2023 showing feasibility of using this method in clinical settings in patients with BPD (Zopfs et al., 2023).

Annex 9

Linhartová, P., Látalová, A., Kóša, B., Kašpárek, T., Schmahl, C., & Paret, C. (2019). fMRI neurofeedback in emotion regulation: A literature review. *Neuroimage,* 193, 75–92. doi: 10.1016/j.neuroimage.2019.03.011

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fMRI neurofeedback in emotion regulation: A literature review

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ABSTRACT

Objectives: Emotion regulation is one of the most prevalent objectives for real-time fMRI neurofeedback (rt-fMRI-NF) studies. The existing studies differ in a number of methodological parameters. This study provides a literature review of the main parameters and results of studies using rt-fMRI-NF for emotion regulation enhancement.
Method: A search of the Web of Science database up through November 8, 2018, identified 144 articles written in English, 89 of which were excluded as irrelevant for this study. The remaining 51 original studies and four secondary analyses of previously published original studies were included in the literature review. The selection of target brain areas, target populations, emotion regulation protocols, NF presentation, control group types, and emotion regulation instructions were examined in relation to achieved brain regulation and changes in cognitive or clinical outcomes. Study results were evaluated in terms of their statistical robustness.
Results: The results show that healthy people are able to regulate their brain activity in the presence of rt-fMRI-NF from various brain regions related to emotion regulation, including the amygdala, anterior insula, and anterior cingulate cortex. The regulation of brain activity using rt-fMRI-NF from prefrontal-limbic connectivity or from individually navigated brain areas is feasible as well. Most studies that used a control group show that rt-fMRI-NF actually induces some effects on brain regulation, cognitive variables, and clinical variables. Generally, the success of ROI regulation during NF training is related to the combination of target brain region, the type of emotion regulation task, and the population undergoing the training. In terms of patient groups, the strongest support for the beneficial effects of rt-fMRI-NF has been shown in increased positive emotion experiencing in patients with depression and in decreased anxiety in patients with anxiety disorders. Symptom reduction following NF training has been also reported in patients with PTSD, BPD, and schizophrenia, but direct comparisons with control groups in these studies makes it impossible to evaluate the added value of NF. Studies often do not report all the relevant analyses for evaluating NF success and many studies lack statistical robustness.
Conclusions: Overall, rt-fMRI-NF seems a promising tool for emotion regulation enhancement with the potential to induce long-term symptom reduction in patients with various mental disorders. Preplanning of statistical analyses, careful interpretations of the results, and evaluations of the NF effect on symptom reduction in patient groups is recommended.

1. Introduction

Real-time fMRI neurofeedback (rt-fMRI-NF) is an innovative tool for learning brain self-regulation. In rt-fMRI-NF studies, the blood-oxygen-level dependent (BOLD) signal from a selected brain area is measured and presented back to a subject in an MRI scanner. The aim of rt-fMRI-NF is to promote the subject's learning self-control over the activity in a selected brain area and, consequently, over the mental state corresponding with the activity in the given brain area. One of the most broadly studied fields within rt-fMRI-NF is emotion regulation. Although a relatively high number of studies focus on this topic, they substantially

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List of abbreviations

rt	real-time
ACC	anterior cingulate cortex
AI	anterior insula
BOLD	blood-oxygen-level dependent
BPD	borderline personality disorder
BVS	best voxel selection
CBT	cognitive behavioral therapy
CG	control group
DLPFC	dorsolateral prefrontal cortex
DMPFC	dorsomedial prefrontal cortex
EG	experimental group
fMRI	functional magnetic resonance imaging
hIPS	horizontal intraparietal sulcus
IFG	inferior frontal gyrus
LPFC	lateral prefrontal cortex
MTL	middle temporal lobe
MVPA	multivariate voxel pattern analysis
NAcc	nucleus accumbens
NF	neurofeedback
OCD	obsessive-compulsive disorder
OFC	orbitofrontal cortex
PTSD	posttraumatic stress disorder
ROI	region of interest
SN/VTA	substantia nigra/ventral tegmental area
SVM	support vector machine
VLPFC	ventrolateral prefrontal cortex

differ in key methodological parameters, such as target brain areas, target populations, emotion regulation protocols, forms of neurofeedback presentation, control groups, and instructions for emotion regulation. The aim of this literature review is to describe the main methodological aspects that need to be considered when starting a new rt-fMRI-NF study in emotion regulation, and, consequently, to promote informed hypotheses generation in future studies in this important and rapidly developing field.

1.1. Brain targets and target populations for emotion regulation with rt-fMRI-NF

Various brain regions can be used for rt-fMRI-NF augmented emotion regulation training because of their differing involvement in emotion processing and emotion regulation (Morawetz et al., 2017). The activity of some regions is associated with the intensity of emotional experiencing; the activity of other regions is associated with the implementation of emotion regulation strategies (Kalisch, 2009; Paret et al., 2011). For example, the amygdala and anterior insula (AI) have been repeatedly found to be involved in experiencing both positive and negative emotions (Kurth et al., 2010; Sergerie et al., 2008). Thus, the amygdala or AI activity levels can be taken as correlates of emotional experiencing intensity, regardless of the emotional valence, i.e. regardless of whether the person experiences positive or negative emotions. On the other hand, lateral prefrontal cortex (LPFC) regions have been repeatedly found to be involved in cognitive emotion regulation (Kohn et al., 2014). Thus, LPFC activity levels can be taken as correlates of cognitive emotion regulation efforts.

NF-aided emotion regulation can be studied in healthy people, but the clinical goal of rt-fMRI-NF is to promote emotion regulation in patients whose ability to regulate emotions is impaired. Emotion regulation impairment is a frequently occurring challenge for patients with different mental disorders, including mood, anxiety, stress, and personality disorders (Kring, 2008). Thus, a focus on enhancing emotion regulation is a key feature in therapy for many psychiatric patients. At the same time, the type of emotion regulation impairment can differ among patient groups (i.e., different brain regions can be affected or the same regions can be affected in a different way). For example, patients with depression show an exaggerated amygdala response to negative stimuli and an attenuated amygdala response to positive stimuli (Groenewold et al., 2013). Accordingly, the goal of rt-fMRI-NF in patients with depression could be to decrease amygdala activity during the experience of negative emotions or to promote amygdala activity while experiencing positive emotions.

1.2. rt-fMRI-NF emotion regulation protocols

Subjects can be instructed to increase (i.e., upregulate) or decrease (i.e., downregulate) their negative or positive emotions by upregulating or downregulating their brain activity. Studies may or may not present additional emotion-evoking stimuli. For example, subjects can be presented with pictures or scripts with emotional content and, subsequently, subjects can be instructed to regulate the evoked emotions using NF information (e.g., Paret et al., 2014). In another approach, subjects can be instructed to regulate their brain activity by implementing an emotion regulation strategy that promotes or reduces the experience of emotions (such as contemplating emotional memories or relaxing) without the use of emotion-evoking stimuli (e.g., Zotev et al., 2011). The directions in which the emotions and the target brain area activity are regulated need to be distinguished. For example, the upregulation of the activity of a region that is not sensitive to emotional valence, such as the amygdala (Sergerie et al., 2008), can be achieved by upregulating either positive or negative emotions. In other regions, a BOLD signal increase may be related to specific emotional experiences. For example, activity in the reward-related brain areas, such as nucleus accumbens (NAcc), is associated with positive, but not negative emotions (Lang and Bradley, 2010).

1.3. Continuous vs. intermittent NF presentation

NF can be presented in either a continuous or intermittent form. Continuous rt-fMRI-NF means that NF is presented throughout the whole task (or respective experimental condition) with signal updates after each repetition time. Continuous NF can be presented e.g. as a continuously updated scale (e.g., Paret et al., 2014) or as a development curve (e.g., Scheinost et al., 2013). Intermittent (or end-of-block) NF is presented as a single outcome after the end of each trial or time interval, e.g. as a single outcome on a scale (e.g., Zilverstand et al., 2015) or as a number (e.g., Sarkheil et al., 2015) representing the level of target brain activity during the previous block. NF can also be presented in more complex ways, such as visual scenes (Lorenzetti et al., 2018). Whether the presentation of continuous or intermittent NF can be more advantageous in some situations remains uncertain. It can be argued that continuous NF provides subjects with more thorough information, and thus can theoretically lead to better training effects. On the other hand, if continuous NF is presented, the simultaneous use of visual emotion-evoking stimuli can possibly draw attention away from NF and diminish the training effects; alternately, it could produce emotion downregulation simply by drawing the subjects' attention away from these stimuli.

1.4. Control groups

Several types of control groups can be used in rt-fMRI-NF studies. Specifically, sham NF can be used; most frequently this is obtained from a different subject (further termed "yoked NF", e.g., Hamilton et al., 2011). Alternately, NF from a region other than the target brain region of a given subject can be presented in the control group (further termed the

"alternate region of interest (ROI) NF", e.g., Zotev et al., 2011). In yoked and alternate ROI NF control groups, the subjects are not aware that the signal they are receiving is not from their target brain area, and thus studies can be blinded. Finally, there can be an absence of NF presentation in the control group (further termed "no NF", e.g., Johnston et al., 2011). Because emotion regulation protocols involve emotion regulation training per se, the use of a control group is crucial for determining whether NF presentation provides an additional learning boost. However, the effect of control group manipulation remains a topic of ongoing debate. Using alternate ROI NF and yoked NF in control groups has the advantage of maintaining comparable motivational aspects as for subjects presented with genuine NF (Thibault et al., 2018). There are also studies showing that the presentation of any feedback is associated with brain activity increase (Emmert et al., 2016; Ninaus et al., 2013) and might produce specific effects that are different from those in control groups presented with no NF. Using control groups with no NF prevents blinding subjects and researchers, and likely increases psychosocial effects. On the other hand, feedback that is not contingent on the subject's target brain area activity has the potential to confuse and frustrate subjects (e.g., Sulzer et al., 2013), thus potentially negatively influencing their motivation and the success of their regulation. Cohen Kadosh et al. (2016) argue that the use of yoked or alternate ROI NF can raise ethical issues, since subjects could reject potentially successful strategies only because they do not correspond with the presented NF.

1.5. Instructions for NF regulation

Subjects may be instructed about strategies they should implement for ROI regulation in greater or lesser detail or not at all. If no specific instruction for emotion regulation is provided, subjects are only instructed to regulate their brain activity according to the NF presentation (Marxen et al., 2016), or subjects can be informed about the nature of the brain area (i.e., that it is related to emotions, e.g., Johnston et al., 2011). If specific instructions for emotion regulation are provided, several emotion regulation strategies may be suggested that subjects can use (e.g., Hamilton et al., 2016), or they may be asked to prepare the strategies before the experiment (e.g., Young et al., 2014), or they may even undergo emotion regulation training before the experiment (e.g., Sarkheil et al., 2015). It is unclear whether the emotion regulation instruction type and level of detail can influence the regulation success. While more detailed instructions or pre-experimental preparation can ensure greater focus on a specific emotion regulation strategy and longer time for training in this strategy during the experiment, providing subjects with space to find their own suitable strategy during the task can theoretically also be beneficial.

1.6. Presentation of regulation success

Studies comprise one or several NF training runs within one or several fMRI sessions. Most often, the NF runs are composed of regulation and control conditions that can include a cognitive task, resting, or watching emotional stimuli without regulating. The success of ROI activity regulation is usually reported as a difference in achieved signal change during the task between the regulation and control conditions, and between the experimental group and the control group in studies that include control groups. In some studies, "transfer runs" are employed after the NF training that involve the same task as during NF training, but without NF presentation. Transfer runs serve to assess the sustainability of training effects after the removal of NF (e.g., Zotev et al., 2011). Some studies also evaluate self-reported cognitive effects or changes in clinical symptoms directly after the NF experiment (e.g., Hamilton et al., 2016) or in long-term aspects (e.g., Rance et al., 2018).

1.7. Objectives

Our objective in this literature review is to present a comprehensive overview of key design parameters of rt-fMRI-NF in emotion regulation studies and to explore the influence of these parameters on brain regulation success and cognitive or clinical changes after rt-fMRI-NF training. Specifically, the review addresses the following research questions:

1. In which *brain areas* has rt-fMRI-NF for emotion regulation been successfully used?
2. In which *populations* has rt-fMRI-NF for emotion regulation been successfully used?
3. Do studies with different *emotion regulation protocols* achieve similar results?
4. Is presentation of *continuous or intermittent* NF for emotion regulation more advantageous?
5. Is any type of *control group* superior to other types?
6. How does the presentation of *instructions for emotion regulation* influence the results?

2. Method

We searched the *Topic* (neurofeedback) AND (fMRI OR functional magnetic resonance imag* OR functional MRI) AND (emot* OR affect*) across all databases and all years in the Web of Science on November 8, 2018, with 125 results. Other potential studies (N = 20) were identified through an additional search. There were two eligibility criteria: 1. Original studies or secondary analyses derived from original studies using the rt-fMRI-NF method, and 2. The use of rt-fMRI-NF for voluntary emotion regulation enhancement. Both criteria needed to be met for the study to be included in the review. Voluntary emotion regulation was defined as the intentional modification of the subject's own present emotional experience. To keep the focus of the review, pain and craving regulation studies were not included, since they constitute more complex phenomena, with emotion regulation being only one possible part of the regulation process. Two authors of this review independently screened the titles and abstracts yielded by the search against the inclusion criteria. After duplicates were removed, 144 articles written in English were identified. We eliminated 52 articles not related to rt-fMRI-NF in the field of emotion regulation (e.g., studies using electroencephalography or functional near-infrared spectroscopy NF, or studies using rt-fMRI-NF not related to emotion regulation), 13 conference abstracts, 7 methodological articles, and 12 reviews or commentaries. The remaining 60 studies' full reports were screened. If any uncertainty about the eligibility of the article arose, it was discussed with the rest of the review authors. Based on this procedure, another five studies that did not meet both eligibility criteria were excluded. Studies that did not claim to be focused on emotion regulation directly, but that clearly instruct subjects to regulate their brain activity using emotion regulation strategies were included in the review (e.g., Caria et al., 2007; Ruiz et al., 2013; Yao et al., 2016). The final pool of papers includes 51 original studies (see Table 2 for the studies overview). Four studies presenting secondary analyses were also included (Paret et al., 2016b; Young et al., 2018, 2017a; Zotev et al., 2013).

2.1. Results presentation

First, the study characteristics were described for each study included in this literature review (Table 2). Second, study parameters were summarized according to our objectives (target brain areas, target populations, emotion regulation protocols, form of NF presentation, and emotion regulation instructions) and displayed, preferably, with figures. Third, study results were summarized. As the studies differ in the type of data analysis, related to differences in study designs, we developed an evaluation system that could be applied to a majority of the included studies (see Table 1 for criteria overview). Since only some studies used corrections for multiple comparisons, we considered the results to be significant if the relevant p value was less than 0.05 uncorrected; thus we maintained the same standard for all studies. If a study only presented

Table 1
Overview of criteria for studies results evaluation.

	ROI regulation (vs. CG)	Training time effect	ROI regulation in transfer task	Cogn./clin. effects vs. baseline (vs. CG)
Y	Sig. diff. between exp. and control condition in: • session average • the last block • the last block of the last session	• Sig. effect of training time on ROI regulation in regression analysis • Sig. diff. between first and last block/session in ROI regulation	Sig. ROI regulation in transfer task	Sig. diff. in cogn./clin. variables in EG after NF training vs. baseline (before NF training)
N	No sig. diff. between exp. and control condition	No sig. effect of training time on ROI regulation AND no sig. diff. between first and last block/session	No sig. ROI regulation in transfer task	No sig. diff. in cogn./clin. variables in EG after NF training vs. baseline (before NF training)
CG++	• Sig. effect of group on ROI regulation in regression analysis • Sig. diff. in ROI regulation between EG and CG (in average or in last block/session)	–	Sig. diff. in ROI regulation in transfer task between EG and CG	Sig. diff. in change in cogn./clin. variables between EG and CG
CG+	Sig. ROI regulation in EG, no sig. ROI regulation in CG	–	Sig. ROI regulation in transfer task in EG, no sig. ROI regulation in transfer task in CG	Sig. change in cogn./clin. variables in EG, no sig. change in cogn./clin. variables in CG
CG-	• No sig. diff. in ROI regulation between EG and CG • Sig. diff. in ROI regulation in both EG and CG	–	• No sig. diff. in ROI regulation in transfer task between EG and CG • Sig. diff. in ROI regulation in transfer task in both EG and CG	• No sig. diff. in change in cogn./clin. variables between EG and CG • Sig. change in cogn./clin. variables in both EG and CG
no CG	no CG used	–	no CG used	no CG used
NR	• results of ROI regulation are not reported	Study presents data for multiple blocks/session, but does not report the effect of training time on ROI regulation	Study involves a transfer task, but does not present results of ROI regulation in transfer task	Cogn./clin. changes were assessed but are not reported
NA	–	only block average analyzed/no time analysis	Study does not involve a transfer task	Cogn./clin. changes were not assessed

Note: Y = yes, N = no, EG = control group, CG = control group, NR = not reported, NA = not assessed, ROI = region of interest, sig. = significant, diff. = difference, exp. = experimental, cogn. = cognitive, clin. = clinical.

results with a correction for multiple comparisons, this is mentioned in a footnote. The study evaluation was performed according to the following criteria (see Table 1 for overview):

- *ROI regulation vs. control condition* describes whether the target ROI activity was significantly different in the regulation condition as compared to the control condition in the desired direction (i.e., higher in upregulation and lower in downregulation). ROI activity regulation in comparison to the control condition was reported as positive if either (1) the subjects significantly regulated the target ROI activity in the desired direction in comparison to the control condition on average for the whole session in studies comprising one session without an analysis of separate blocks within the session, or (2) the subjects significantly regulated the target ROI activity in the desired direction in comparison to the control condition in the last training block in studies with one session comprising multiple blocks, or (3) the subjects significantly regulated the target ROI activity in the desired direction in comparison to the control condition in the last session on average or in the last block of the last session in studies comprising multiple sessions.
- *ROI regulation vs. control group* describes whether the subjects in the experimental group regulated the target ROI activity significantly better than the subjects in the control group (under the condition that the experimental group did regulate the ROI activity successfully). ROI regulation vs. control group was reported as positive if either (1) there was a significant effect of group on ROI activity regulation in regression analysis, or (2) ROI activity regulation was significantly more successful in the experimental group than in the control group on average in studies without analysis of separate blocks/sessions, or (3) ROI activity regulation was significantly more successful in the experimental group than in the control group in the last block/session in studies analyzing separate blocks/sessions. Because a number of studies do not provide a direct comparison of experimental and control groups, we rated the ROI regulation vs. control group as positive also if (4) there was significant ROI activity regulation in the experimental group, but not in the control group (either on average, or in the last block/session). The evaluation was complemented by "++" if the study directly evaluated the group differences (either in regression analysis, or by t-tests, criterion 1, 2, or 3 met), and by "+" if the study only provided separate results for experimental and control groups (criterion 4 met) to reflect the robustness of the results (see Table 1).
- *Training time effect* describes whether the subjects improved in ROI activity regulation across the NF training course in studies comprising multiple blocks or/and sessions, where ROI activity regulation is defined as a significant difference in regulation and control condition. Hence, the training effect was evaluated as positive if (1) there was a significant effect of training time (either across training blocks or across training sessions) on the ROI activity regulation if regression analysis of the training time effect was reported, or (2) if the ROI activity regulation significantly increased from the first block/session to the last block/session.
- *Transfer effect* was evaluated as positive if there was successful ROI activity regulation in a transfer block, i.e. in a block without NF presentation and following NF training. In studies with a control group, we also evaluated whether there was significant difference in ROI activity regulation in the transfer run between the experimental and control groups (see Table 1).
- Finally, *cognitive or clinical effects vs. baseline or/and control group* was rated positive if there was a significant effect on cognitive or clinical variables in the experimental group following the NF training. A positive result was recorded if there was a difference in cognitive or clinical variables from baseline (i.e., before NF training). If a study included a control group, we also recorded whether there was a significant difference in the effect between the experimental and control groups (see Table 1).

Table 2
Review of rt-fMRI-NF in emotion regulation study parameters.

Study	Target region (localization)	Task (ROI)	Task (emotions)	Population	NF I/C	Control group	Sample size	Additional stimuli	Instructions for emotion regulation
Berman et al. (2013)	right anterior insula (functional: blink suppression task)	up	unspecified upregulation	healthy subjects	C	none	14	none	autobiographical mental imagery
Brühl et al. (2014)	right amygdala (functional: watching negative vs. neutral pictures)	down	negative downregulation	healthy subjects	C	none	6	fearful, sad and angry faces	cognitive reappraisal
Buyukturkoglu et al. (2015)	bilateral anterior insula (anatomical + functional: watching symptom-provoking vs. neutral pictures)	down	negative downregulation	patients with OCD	I	none	3	contamination-related pictures	find a cognitive strategy
Caria et al. (2007)	right anterior insula (anatomical)	up	unspecified upregulation	healthy subjects	C	multiple: 1) no NF, 2) alternate ROI NF (large background region)	9 (EG) +3 (CG1) +3 (CG2)	none	autobiographical mental imagery
Caria et al. (2010)	left anterior insula (anatomical)	up	unspecified upregulation	healthy subjects	C	multiple: 1) no NF, 2) alternate ROI NF (large background region)	9 (EG) +9 (CG1) +9 (CG2)	none	autobiographical mental imagery
Cohen Kadosh et al. (2016)	bilateral insula (functional: emotional Go/NoGo task)	up, down	positive upregulation, unspecified downregulation	healthy children and adolescents (age 7 to 16)	C	none	17	none	happy mental imagery/ relaxation
Gerin et al. (2016)	bilateral amygdala (functional: watching/hearing anxiety-provoking stimuli)	down	negative downregulation	patients with PTSD	C	none	3	personalized trauma scripts (audio recordings)	none (but information about ROI provided)
Greer et al. (2014)	bilateral nucleus accumbens (anatomical)	up, down	positive upregulation, unspecified downregulation	healthy women	C	none	25	none	mental imagery of exciting/boring events
Gröne et al. (2014a)	anterior ACC (anatomical)	up	unspecified upregulation	healthy subjects	C	comparing 3T and 7T scanners	24 (15 in 3T scanner group scanning + 9 in 7T scanner group))	none	mental imagery, concentration on bodily sensations
Hamilton et al. (2011)	subgenual ACC (functional: watching negative images vs. baseline)	down	positive upregulation	healthy subjects	C	yoked NF	8 (EG) +9 (CG)	none	increase positive mood
Hamilton et al. (2016)	individual (functional: watching negative pictures, resulting in AI, OFC, dorsal ACC, or IFG)	down	negative downregulation	women with major depressive disorder	I	yoked NF	10 (EG) +10 (CG)	aversive pictures	cognitive reappraisal, attentional redirection, mental imagery
Hellrung et al. (2018)	left amygdala (anatomical)	up	positive upregulation	healthy men	C, I	continuous NF vs. intermittent NF vs. no NF	16 (continuous) +18 (intermittent) + 8 (no NF)	none	positive autobiographical mental imagery
Herwig et al. (2019)	amygdala (functional: watching negative vs. neutral pictures)	down	negative downregulation	healthy subjects	C	random values	15 (EG) +11 (CG)	aversive pictures	cognitive reappraisal
Johnston et al. (2010)	individual (functional: watching negative vs. neutral pictures, resulting in VLPFC/insula, or MTL incl. amygdala)	up	unspecified upregulation	healthy subjects	C	none	13	none	emotional imagery
Johnston et al. (2011)	individual (functional: watching positive vs. neutral pictures, resulting in VLPFC, DLPFC, insula, or MTL)	up	unspecified upregulation	healthy subjects	C	no NF	17 (EG) +10 (CG)	none	none (but information about ROI selection procedure provided)
Koush et al. (2017)	connectivity from DMPFC onto bilateral amygdala	up	positive upregulation	healthy subjects	I	yoked NF	9 (EG) +6 (CG)	pictures of positive social situations/ nonsocial neutral objects	mental imagery (experiencing the social situation)
Lawrence et al. (2014)	right anterior insula (anatomical)	up	unspecified upregulation	healthy subjects	C	alternate ROI NF (middle parahippocampal region)	16 (EG) +8 (CG)	none	positive/negative autobiographical mental imagery or interceptive awareness

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Table 2 (*continued*)

Study	Target region (localization)	Task (ROI)	Task (emotions)	Population	NF I/C	Control group	Sample size	Additional stimuli	Instructions for emotion regulation
Li et al. (2016a)	individual (MVPA of happy/sad mental imagery)	up	unspecified upregulation	healthy subjects	C	none	12	none	positive/negative autobiographical mental imagery
Li et al. (2016b)	individual (MVPA of happy/sad mental imagery)	up	positive upregulation	healthy subjects	C	no NF	12 (EG) +11 (CG)	none	positive autobiographical mental imagery
Linden et al. (2012)	individual (functional: watching positive vs. neutral pictures, resulting in VLPFC, insula or DLPFC)	up	positive upregulation	patients with current major depressive episode	C	outside the scanner	8 (EG) +8 (CG)	none	positive autobiographical mental imagery
Lorenzetti et al. (2018)	individual (tenderness vs. neutral and anguish vs. neutral contrast, 2 methods: ROI and SVM)[a]	up	positive and negative upregulation	healthy subjects	C	none	8	none	feel tenderness/anguish intensely
MacDuffie et al. (2018)	ACC (functional: negative upregulation vs. (negative downregulation + count) contrast)	up, down	negative upregulation and downregulation	patient with depression after CBT treatment	I	none	13	none	individual strategies training
Marxen et al. (2016)	bilateral amygdala (anatomical)	up, down	unspecified upregulation and downregulation	healthy subjects	C, I	none	33	none	none
Mehler et al. (2018)	individual (functional: watching positive vs. neutral pictures, resulting in limbic and frontal areas)	up	positive upregulation	patients with depression	C	alternate ROI NF (parahippo-campal area)	16 (EG) +16 (CG)	none	positive mental imagery
Misaki et al. (2018)[b]	left amygdala (anatomical)	up	positive upregulation	war veterans with and without PTSD	C	alternate ROI NF (hIPS)	non-PTSD veterans: 17 (EG) [+PTSD veterans: 21 (EG) +9 (CG)]	none	positive autobiographical mental imagery
Moll et al. (2014)	individual (SVM based patterns for tenderness/affection vs. pride-related autobiographical memories)	up	tenderness/ affection or pride upregulation	healthy subjects	C	no NF	12 (EG) +12 (CG)	none	tenderness/affection or pride-evoking autobiographical mental imagery
Nicholson et al. (2017)	bilateral amygdala (anatomical + functional BVS: watching trauma-related vs. neutral words)	down	negative downregulation	patients with PTSD	C	none	10	personalized trauma words	regulate the brain feeling center
Nicholson et al. (2018)[c]	bilateral amygdala (anatomical + functional BVS: watching trauma-related vs. neutral words)	down	negative downregulation	patients with PTSD	C	none	14	personalized trauma words	regulate the brain feeling center
Paret et al. (2014 + 2016b)	bilateral amygdala (anatomical + functional BVS: watching negative vs. neutral pictures)	down	negative downregulation	healthy women	C	alternate ROI NF (rostral caudate)	16 (EG) +16 (CG)	aversive pictures	regulate the brain feeling center
Paret et al. (2016a)	bilateral amygdala (anatomical + functional BVS: watching negative vs. neutral pictures)	down	negative downregulation	women with borderline personality disorder	C	none	8	aversive pictures	regulate the brain feeling center
Paret et al. (2018)	right amygdala (anatomical)	up, down	negative upregulation and downregulation	healthy women	C	none	20	aversive pictures	none
Posse et al. (2003)	bilateral amygdala (anatomical)	up	negative upregulation	healthy subjects	I	none	6	sad and neutral faces	sad autobiographical mental imagery
Rance et al. (2018)	individual (functional: watching neutral vs. symptom provoking	up, down	negative upregulation and downregulation	patients with OCD	C	yoked NF	10 (EG) +7 (CG)	OCD symptom-provoking pictures	none (but information about ROI provided)

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Table 2 (*continued*)

Study	Target region (localization)	Task (ROI)	Task (emotions)	Population	NF I/C	Control group	Sample size	Additional stimuli	Instructions for emotion regulation
	pictures, resulting in orbitofrontal/ ventral frontopolar cortex)								
Ruiz et al. (2013)	bilateral insula (functional: autobiographical mental imagery vs. rest)	up	unspecified upregulation	patients with paranoid schizophrenia	C	none	9	none	autobiographical mental imagery
Sarkheil et al. (2015)	left LPFC (functional: regulate vs. watch aversive pictures)	up	negative downregulation	healthy subjects	I	no NF	8 (EG) +6 (CG)	aversive pictures	cognitive reappraisal training
Scheinost et al. (2013)	orbitofrontal cortex (functional: watching neutral vs. contamination pictures)	up, down	negative upregulation and downregulation	subjects with sub-clinical contamination anxiety	C	yoked NF	10 (EG) +10 (CG)	contamination-related pictures	preparation of strategies with a clinical psychologist before the experiment
Scheinost et al. (2014) [d]	orbitofrontal cortex (functional: watching neutral vs. contamination pictures)	up, down	negative upregulation and downregulation	patients with OCD	C	none	5	contamination-related pictures	preparation of strategies with a clinical psychologist before the experiment
Sitaram et al. (2014)	left anterior insula (functional: autobiographical mental imagery vs. counting task)	up	negative upregulation	sexual offenders	C	none	4	none	negative autobiographical mental imagery
Sulzer et al. (2013)	substantia nigra/ventral tegmental area (anatomical)	up	positive upregulation	healthy subjects	C	inverted NF	15 (EG) +17 (CG)	none	rewarding mental imagery
Veit et al. (2012)	left anterior insula (functional: watching negative pictures vs. rest)	up, down	negative upregulation and downregulation	healthy subjects	C	none	11	threat-related pictures	imagery of being involved in/absent from the aversive pictures
Weiskopf et al. (2003)	rostral—ventral ACC + dorsal ACC (anatomical)	up, down	unspecified upregulation and downregulation	healthy subject	C	none	1	none	none
Yao et al. (2016)	left anterior insula (functional: watching painful vs. neutral pictures)	up	negative upregulation	healthy subjects	C	alternate ROI NF (background region)	18 (EG) +14 (CG)	none	negative autobiographical mental imagery
Young et al. (2014)	left amygdala (anatomical)	up	positive upregulation	patients with current major depressive episode	C	alternate ROI NF (hIPS)	14 (EG) +7 (CG)	none	positive autobiographical mental imagery
Young et al. (2017b + 2017a, 2018)	left amygdala (anatomical)	up	positive upregulation	patients with current major depressive episode	C	alternate ROI NF (hIPS)	19 (EG) +17 (CG)	none	positive autobiographical mental imagery
Yuan et al. (2014)	left amygdala (anatomical)	up	positive upregulation	patients with current major depressive episode	C	alternate ROI NF (hIPS)	27 (EG) +27 (CG)	none	positive autobiographical mental imagery
Zilverstand et al. (2015)	right anterior insula (functional: watching spider pictures vs. rest) + left DLPFC (functional: regulate spider pictures vs. rest)	down (insula) + up (DLPFC)	negative downregulation	women with spider phobia	I	no NF	9 (EG) +9 (CG)	spider pictures	cognitive reappraisal training
Zotev et al. (2011 + 2013)	left amygdala (anatomical)	up	positive upregulation	healthy subjects	C	alternate ROI NF (hIPS)	14 (EG) +14 (CG)	none	positive autobiographical mental imagery
Zotev et al. (2014) [e]	left amygdala (anatomical)	up	positive upregulation	healthy subjects	C	none	6	none	positive autobiographical mental imagery
Zotev et al. (2016)	left amygdala (anatomical)	up	positive upregulation	patients with current major depressive episode	C	alternate ROI NF (left hIPS)	13 (EG) +11 (CG)	none	positive autobiographical mental imagery
Zotev et al. (2018)	left amygdala (anatomical)	up	positive upregulation	patients with PTSD	C	alternate ROI NF (hIPS)	20 (EG) +11 (CG)	none	positive autobiographical mental imagery

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Table 2 (*continued*)

Study	Target region (localization)	Task (ROI)	Task (emotions)	Population	NF I/C	Control group	Sample size	Additional stimuli	Instructions for emotion regulation
Zweerings et al. (2018)	ACC (anatomical)	up	positive upregulation	patients with PTSD + healthy controls	C	none	9 (EG) +9 (CG: healthy controls)	none	positive mental imagery, concentration on bodily sensations

Note: ACC = anterior cingulate cortex, AI = anterior insula, BVS = best voxel selection, CBT = cognitive behavioral therapy, CG = control group, ACC = anterior cingulate cortex, DLPFC = dorsolateral prefrontal cortex, DMPFC = dorsomedial prefrontal cortex, EG = experimental group, hIPS = horizontal intraparietal sulcus, I/C = intermittent/continuous, IFG = inferior frontal gyrus, LPFC = lateral prefrontal cortex, MTL = medial temporal lobe, MVPA = multivariate voxel pattern analysis, NF = neurofeedback, OCD = obsessive-compulsive disorder, OFC = orbitofrontal cortex, PTSD = posttraumatic stress disorder, ROI = region of interest, SVM = support vector machine, VLPFC = ventrolateral prefrontal cortex.

[a] ROI method resulted in septohypothalamic area for tenderness vs. neutral contrast and right amygdala for anguish vs. neutral contrast.

[b] Study includes original data from 17 war veterans without PTSD and additional analyses of data from 30 war veterans with PTSD (21: EG, 9: CG) previously published in Zotev et al. (2018).

[c] 10 out of 14 subjects are the same subjects whose data was already presented in Nicholson et al. (2017).

[d] Only originally obtained data are reported for this study; however, the study also presents a secondary analysis of data from 10 subjects with sub-clinical contamination anxiety (only experimental group) from a study by Scheinost et al. (2013).

[e] This study used simultaneous fMRI and EEG neurofeedback presentation.

3. Results

Study characteristics are described in Table 2.

3.1. Target brain areas and target populations

Fig. 1 shows a representation of target brain regions and target populations.

3.2. Emotion regulation protocols

Fig. 2 shows the distribution of emotion regulation protocols (downregulation vs. upregulation and use of additional emotion-evoking stimuli). If a study used more than one regulation condition (e.g., negative downregulation and negative upregulation), it is included in all respective categories in Fig. 2. Studies that instructed the subjects to increase the intensity of emotions without specifying the emotional valence, and studies that instructed the subjects to regulate the NF scale directly without further specification are referred to as "unspecified upregulation" in Table 2 and Fig. 2. Studies that instructed the subjects to downregulate emotions without specifying the emotional valence (i.e., to generally detach from emotional experiences or simply "calm down emotionally") and studies that instructed the subjects to downregulate the NF scale directly without further specification are referred to as "unspecified downregulation" in Table 2 and Fig. 2.

3.3. Continuous vs. intermittent NF presentation

Most studies (k = 42) presented NF as a continuous scale, updated with every newly acquired brain scan. K = 7 studies presented intermittent NF. Hellrung et al. (2018) directly compared the use of continuous and intermittent NF, and Marxen et al. (2016) presented continuous NF to the subjects in the first two blocks followed by a third block with intermittent NF.

3.4. Control groups

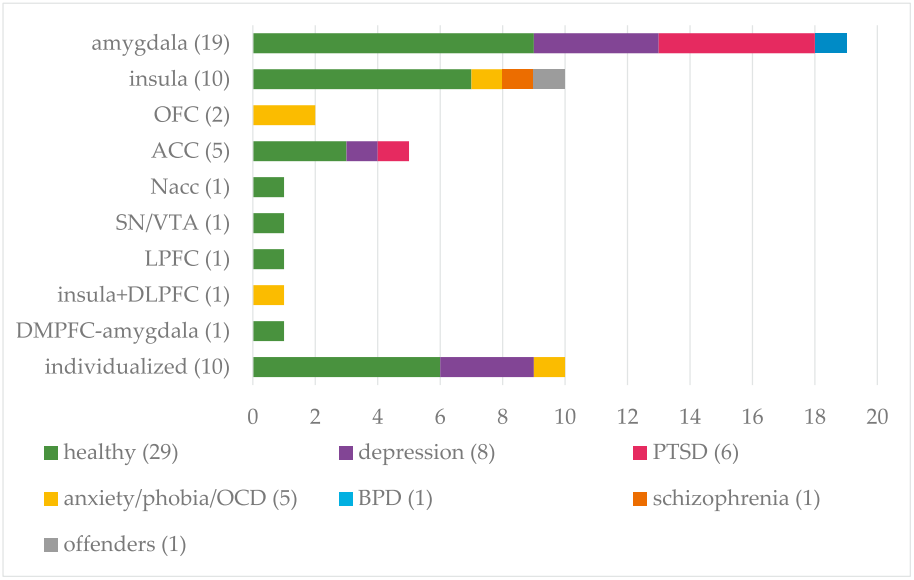
Fig. 3 shows the distribution of control groups.

3.5. Instructions for emotion regulation

Fig. 4 shows the distribution of instructions provided to subjects. If multiple instruction options were given in one study, the study is included in all relevant categories in Fig. 4.

3.6. Evaluation of study results

Table 3 presents the evaluation of the results of studies with a predefined target brain area, structured according to the target brain areas, target populations, and emotion regulation protocols (i.e., direction of ROI regulation, direction and valence of emotions to regulate, presentation of emotion-evoking stimuli, and number of fMRI sessions including NF training). Table 4 presents the evaluation of the results of studies with individually navigated brain targets. Pilot studies with six or fewer subjects were not included in Tables 3 and 4 because the small sample size prevented statistical evaluation (Buyukturkoglu et al., 2015; Gerin et al., 2016; Scheinost et al., 2014; Sitaram et al., 2014; Weiskopf et al., 2003; Zotev et al., 2014). Moreover, Rance et al. (2018) was not included as the results are not presented separately for the group performing emotion regulation NF training.



Note: ACC = anterior cingulate cortex, BPD = borderline personality disorder, DLPFC = dorsolateral prefrontal cortex, DMPFC = dorsomedial prefrontal cortex, LPFC = lateral prefrontal cortex, Nacc = nucleus accumbens, OCD = obsessive-compulsive disorder, OFC = orbitofrontal cortex, PTSD = posttraumatic stress disorder, SN/VTA = substantia nigra/ventral tegmental area

Fig. 1. Target brain regions and populations.
Note: ACC = anterior cingulate cortex, BPD = borderline personality disorder, DLPFC = dorsolateral prefrontal cortex, DMPFC = dorsomedial prefrontal cortex, LPFC = lateral prefrontal cortex, Nacc = nucleus accumbens, OCD = obsessive-compulsive disorder, OFC = orbitofrontal cortex, PTSD = posttraumatic stress disorder, SN/VTA = substantia nigra/ventral tegmental area.

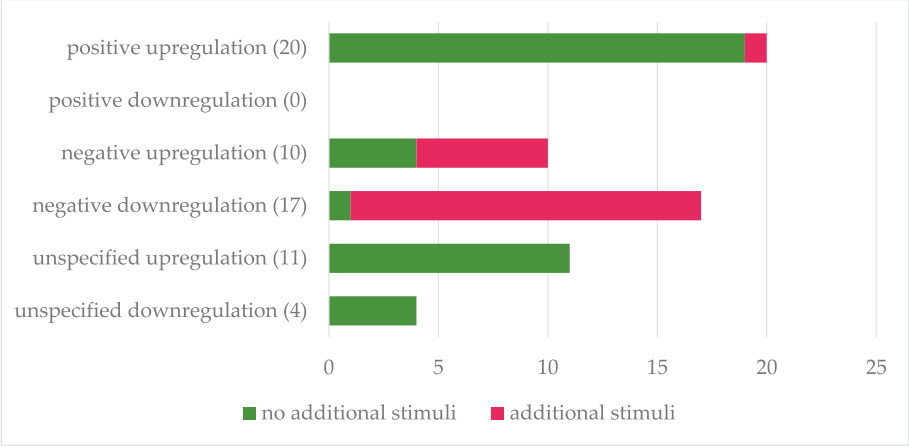


Fig. 2. Emotion regulation tasks and emotional stimuli presentation.

4. Discussion

4.1. Brain targets and populations

4.1.1. Amygdala

Healthy people as well as patients with depression have been found to upregulate activity in the amygdala by increasing positive emotions at rates higher than control groups in all studies that reported an intergroup comparison (see Table 3). In all of these studies, training and transfer effects were also positive (if assessed). Moreover, three out of four studies in patients with depression found significant improvement in depression, anxiety, or happiness over the control groups. PTSD patients upregulated amygdala activity by increasing positive emotions only in the first out of three sessions in a study by Zotev et al. (2018), but a decrease in PTSD symptoms was found after the training, although this was not different from the control group. Amygdala upregulation by increasing negative emotions was explored in two studies (see Table 3); only the subjects in the study by Posse et al. (2003) achieved ROI upregulation. Subjects in this study may have been successful in regulation due to the choice of baseline condition, which consisted of watching neutral pictures (in comparison to watching negative pictures in the experimental condition), as opposed to the study by Paret et al. (2018), in which negative amygdala upregulation was not successful in comparison to the baseline consisting of watching negative pictures. Moreover, the subjects in the study by Paret et al. (2018) performed both upregulation and downregulation tasks within one session, which might be more challenging, and it could require more time than a single session to learn amygdala regulation.

Downregulation of the amygdala by decreasing negative emotions has been found successful in healthy people (except in the 2018 study by Paret et al., see above) and in patients with BPD and PTSD (see Table 3). However, only two of these studies employed a control group and they show a different pattern of intergroup comparison. While healthy people in the study by Herwig et al. (2019) did downregulate amygdala activity significantly better than the control group, there was no difference in amygdala downregulation between the groups of healthy people in the

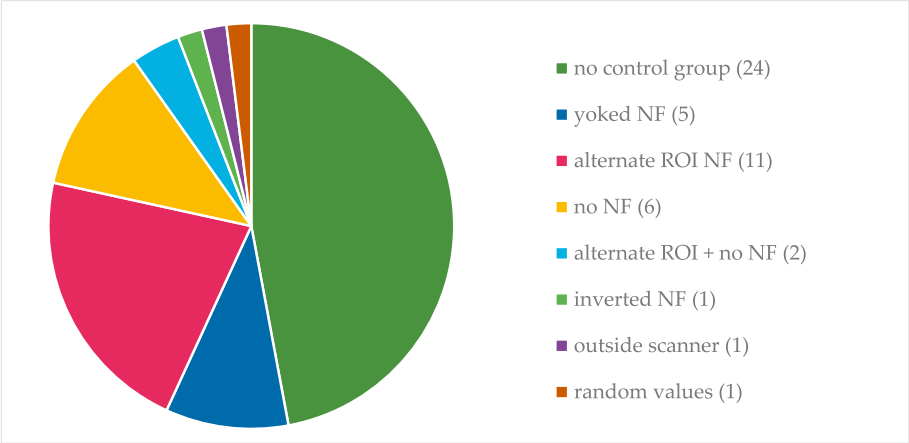


Fig. 3. Control groups.

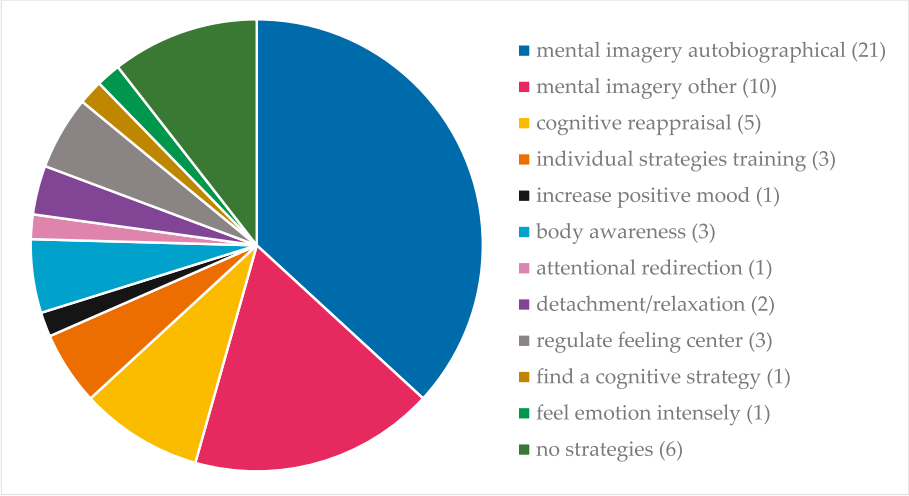


Fig. 4. Instructions for emotion regulation strategies.

study by Paret et al. (2014). However, the experimental group in this study was successful in amygdala downregulation in transfer run, unlike the control group. Also note that the subjects in this study only underwent a single NF session, while the subjects in the study by Herwig et al. (2019) were training for four sessions. Thus, a longer time provided for NF training can naturally lead to stronger ROI regulation in experimental groups. Moreover, the clinical effects of NF training were evaluated by Paret et al. (2016a). A decrease in dissociation and an increase in emotional awareness was found following the NF training in patients with BPD, but comparison with a control group is lacking.

In sum, NF has been shown to promote amygdala upregulation by increasing positive emotions in both healthy people and patients with depression. NF training has also shown amygdala upregulation improvement lasting after the removal of NF and clinical symptom improvement in the patients with depression. Successful amygdala downregulation by decreasing negative emotions while using NF has been observed in healthy people and patients with BPD and PTSD, though control groups are lacking in most of these studies.

4.1.2. Anterior insula

Most studies of AI upregulation do not distinguish between positive and negative emotional upregulation strategies (i.e., unspecified upregulation). All of these studies found successful AI upregulation in healthy people in comparison to control conditions as well as to control groups (where available). Successful AI upregulation was also found in patients with schizophrenia (Ruiz et al., 2013) where the training led to improvement in emotion recognition (without control group involvement). AI upregulation by direct instruction to upregulate negative emotions has been found to be successful in healthy people in two studies. One of these studies involved a control group and found the NF in the experimental group led to more successful AI upregulation as compared to control group (Yao et al., 2016). AI upregulation by increasing negative emotions was also explored in sexual offenders (Sitaram et al., 2014). Only four subjects participated in this study and only one of them upregulated AI. The sample size in this study was too low to draw definite conclusions; however, NF training can be possibly more challenging and require more training time and motivation in this clinical group.

On the other hand, AI downregulation seems to be more challenging, with only one study demonstrating successful AI downregulation by decreasing negative emotions in subjects with spider phobia (Zilverstand et al., 2015). NF in the experimental group in this study led to more successful AI downregulation in comparison to the control group as well as to a larger long-term decrease in spider phobia-related anxiety. Unlike the other studies of AI downregulation, Zilverstand et al. (2015) presented the subjects with AI NF and also with PFC NF, which may have influenced the regulation success. Moreover, the studies that either did not find or did not report the AI downregulation as compared to the control condition used both downregulation and upregulation within one study. The results of the study by Cohen Kadosh et al. (2016) are difficult

Table 3
Evaluation of the results of studies with predefined brain targets in relation to target brain area, target population, and emotion regulation protocols.

Region	Task	Emotions	Population	Studies	Emotional stimuli	NF sessions	ROI regulation (vs. CG)	Training time effect	Transfer effect	Cogn./clin. effects vs. baseline (and CG)
amygdala	up	positive up	healthy	Hellrung et al. (2018)	N	1	NR	NR	Y (CG ++)	NA
				Zotev et al. (2011)	N	1	Y (CG++)	Y	Y (CG ++)	NA
			depression	Young et al. (2014)	N	1	Y (CG ++)	Y	Y (CG ++)	Y (CG ++)
				Young et al. (2017b)	N	2	Y (CG ++)	NR	Y (CG ++)	Y (CG ++)
				Yuan et al. (2014)	N	1	NR	NR	NR	Y (CG -)
				Zotev et al. (2016)[a]	N	1	N (CG ++)	Y	Y (CG +)	Y (CG, ++)
			PTSD	Misaki et al. (2018)	N	3	NR	NR	NR	Y (CG +)
				Zotev et al. (2018)	N	3	N[b] (CG -)	N	N	Y (CG +)
		negative up	healthy	Paret et al. (2018)	Y	1	N[c] (no CG)	NR	NA	NA
				Posse et al. (2003)	Y	1 to 5	Y (no CG)	NA	NA	NA
		unspec. up	healthy	Marxen et al. (2016)	N	3	N (no CG)	N	N[d]	NA
	down	negative down	healthy	Brühl et al. (2014)	Y	4	Y (no CG)	Y	NA	NA
				Herwig et al. (2019)	Y	4	Y (CG ++)	Y	N[e]	NA
				Paret et al. (2014)	Y	1	Y (CG -)	NR	Y (CG +)	NA
				Paret et al. (2018)	Y	1	N[f] (no CG)	NR	NA	NA
			BPD	Paret et al. (2016a)	Y	4	Y (no CG)	NR	N	Y (no CG)
			PTSD	Nicholson et al. (2017)	Y	1	Y (no CG)	N	Y	NA
				Nicholson et al. (2018)	Y	1	Y (no CG)	N	Y	NA
		unspec. down	healthy	Marxen et al. (2016)	N	3	N (no CG)	N	Y	NA
anterior insula	up	positive up	healthy	Cohen Kadosh et al. (2016)	N	4	NA[g] (no CG)	N	NA	NA
		negative up	healthy	Veit et al. (2012)	Y	1	Y (no CG)	N	NA	NA
				Yao et al. (2016)	N	1	Y (CG ++)	Y	Y (CG ++)	Y (CG ++)
		unspec. up	healthy	Berman et al. (2013)	N	1	Y (no CG)	N	N	NA
				Caria et al. (2007)	N	1	Y (CG +)	Y	Y (CG NA)	NA
				Caria et al. (2010)	N	1	Y (CG ++)	Y	NA	Y (CG ++)
				Lawrence et al. (2014)	N	1	Y (CG ++)	Y	NA	N
			schizophrenia	Ruiz et al. (2013)	N	4	Y (no CG)	Y	N	Y (no CG)
	down	negative down	healthy	Veit et al. (2012)	Y	1	N[h] (no CG)	N	NA	NA
		negative down	spider phobia	Zilverstand et al. (2015)	Y	1	Y (CG ++)	Y	NA	Y (CG ++)
		unspec. down	healthy	Cohen Kadosh et al. (2016)	N	4	NA[f] (no CG)	N	NA	NA
ACC	up	positive up	PTSD	Zweerings et al. (2018)[i]	N	3	Y (no CG)	Y	Y (no CG)	Y (no CG)
		unspec. up	healthy	Gröne et al. (2014a)	N	1	Y (no CG)	Y	NA	Y
	down	positive up	healthy	Hamilton et al. (2011)	N	1	Y (CG ++)	N	N	NA
		negative down	depression	MacDuffie et al. (2018)	N	1	NR (no CG)	NR	NA	Y
OFC	up + down	negative up + down	contam. anxiety	Scheinost et al. (2013)	Y	2	NR	NR	NR	Y (CG ++)
NAcc	up	positive up	healthy	Greer et al. (2014)	N	1	Y (no CG)	N	N	NA
	down	unspec. down	healthy	Greer et al. (2014)	N	1	N (no CG)	N	N	NA
SN/VTA	up	positive up	healthy	Sulzer et al. (2013)	N	1	Y/N[j] (CG +)	N	Y	NA

(*continued on next page*)

Table 3 (*continued*)

Region	Task	Emotions	Population	Studies	Emotional stimuli	NF sessions	ROI regulation (vs. CG)	Training time effect	Transfer effect	Cogn./clin. effects vs. baseline (and CG)
PFC	up	negative down	healthy	Sarkheil et al. (2015)	Y	1	NR (CG -)	NR	NA	N
			spider phobia	Zilverstand et al. (2015)	Y	1	Y (CG -)	N	NA	Y (CG ++)
PFC-limbic connectivity	up	positive up	healthy	Koush et al. (2017)	Y	3	Y (CG ++)	Y	Y (CG ++)	Y (CG ++)

Y = yes, N = no, NA = not assessed, NR = not reportedACC = anterior cingulate cortex, AI = anterior insula, BPD = borderline personality disorder, CG = control group, clin. = clinical, cogn. = cognitive, contam. = contamination, NAcc = nucleus accumbens, OCD = obsessive-compulsive disorder, OFC = orbitofrontal cortex, PFC = prefrontal cortex, PTSD = posttraumatic stress disorder, ROI = region of interest, SN/VTA = substantia nigra/ventral tegmental area, unspec. = unspecified.

[a] Results FDR corrected.

[b] ROI regulation significant only in the first out of three sessions.

[c] Refers to comparison with control "view" condition; ROI upregulation was significant in comparison with "down" condition.

[d] Refers to comparison with "rest" condition; ROI upregulation was significant in comparison with "down" condition in transfer run.

[e] As compared to baseline task performed before NF training.

[f] Refers to comparison with control "view" condition; ROI downregulation was significant in comparison with "up" condition.

[g] Only comparison of downregulation vs. upregulation conditions available.

[h] Refers to comparison with "no-regulation" condition, comparison with "up-regulation" condition was significant.

[i] No relevant CG for evaluation of the NF effect, CG included healthy participants who underwent the same procedure as participants in the EG.

[j] Yes based on average results per three runs; No based on the results from the last run.

to interpret because no neutral control condition was used. However, the subjects in the study by Veit et al. (2012) demonstrated successful AI upregulation, but not downregulation, suggesting that downregulating AI could be more challenging than upregulating it.

In sum, NF has been found to promote AI upregulation in healthy people. AI upregulation with the use of NF has also been found successful in patients with schizophrenia, but comparison with a control group is needed. AI downregulation, in contrast, seems to be more challenging, but still possible, as demonstrated by successful AI downregulation in phobia patients, associated with long-term anxiety decreases, as compared to a control group (Zilverstand et al., 2015).

4.1.3. Other regions related to emotional arousal

ACC has been successfully upregulated with the use of NF in healthy people (Gröne et al., 2014b) and in patients with PTSD (Zweerings et al., 2018) in which the NF training also led to decreased PTSD symptoms. Moreover, NF led to more successful ACC downregulation in an experimental group as compared to a control group in healthy people (Hamilton et al., 2011). Note that ACC upregulation (Zweerings et al., 2018) and downregulation (Hamilton et al., 2011; subgenual ACC) was achieved by the same strategy, specifically by increasing positive emotions. This fact probably relates to functional differentiation of ACC subparts (Stevens et al., 2011) which should be addressed in rt-fMRI-NF studies using ACC.

OFC has been selected as a suitable region for rt-fMRI-NF training in patients with OCD because of its hyperactivity associated with OCD symptoms (Mataix-Cols et al., 2004, 2003). The respective studies (Scheinost et al., 2014, 2013) used a design in which the subjects were trained to both downregulate and upregulate the OFC to achieve better general control over it (Hampson et al., 2012). Regulation success for OFC downregulation and upregulation in comparison to control conditions was not presented in these studies; however, the training led to significant long-term decreases in anxiety in subjects with contamination anxiety as compared to the control group (Scheinost et al., 2013), and to some decrease in anxiety in patients with OCD which was not statistically evaluated because of the small sample size (Scheinost et al., 2014).

Finally, upregulation of dopaminergic reward-related areas was found to be successful with positive emotion upregulation in healthy people in two studies (Greer et al., 2014; Sulzer et al., 2013). Downregulation of these regions seems to be more challenging, as demonstrated by unsuccessful downregulation as compared to control conditions in Greer et al. (2014).

4.1.4. Prefrontal cortex

NF did not yield augmented PFC-regulation in two studies that explored this issue (see Table 3). The results suggest that the PFC can be regulated with or without NF, but that subjects do not regulate the PFC better with PFC NF presentation. However, although subjects with spider phobia did not regulate the PFC more than the control group in Zilverstand et al. (2015), the presence of the PFC NF signal may have influenced the successful AI and anxiety downregulation observed in this study. Similarly, in Sarkheil et al. (2015), the subjects did not regulate the PFC more than the control group, but amygdala activity was significantly lower in the experimental group who trained emotion regulation with PFC NF as compared to the control group. Koush et al. (2017) presented NF not separately from the PFC, but directly from prefrontal-limbic connectivity, which was found to represent cognitive emotion regulation ability (Ochsner et al., 2012). The authors found that healthy people were able to upregulate connectivity between DMPFC and the amygdala more successfully than the control group. In sum, it seems that the PFC regulation is not improved by NF, but that presentation of NF from the PFC might improve regulation of other regions, such as the amygdala or insula.

4.1.5. Individualized target areas

Some studies did not use a predefined region from which to present NF, but instead located target regions individually by functional navigation. This approach may result in NF more closely corresponding with a specific function/emotion and may overcome individual differences in functional localization. On the other hand, interpretation of the results is more difficult, because subjects regulate different neural patterns within one study, not necessarily confined to a particular brain region (see Table 4). Brain targets in these studies are navigated either by the BOLD signal contrast between watching emotional vs. neutral pictures, or by the BOLD signal corresponding to emotional imagery. The resulting brain targets are usually located within areas such as the insula, amygdala, ACC, or various PFC regions (see Table 4). In some studies, a corresponding brain network pattern rather than a single target region has been found by computational methods and used for NF (Li et al., 2016a, 2016b; Lorenzetti et al., 2018; Moll et al., 2014). In all of these studies with available respective analyses, the successful regulation of brain targets in comparison to control conditions and control groups has been observed with one exception (Mehler et al., 2018; see Table 4). Thus, individual navigation of brain targets for NF generally leads to successful ROI regulation in healthy people which seems to be augmented by NF.

Table 4
Evaluation of the results of studies with individually navigated brain targets in relation to functional navigation type, target population, and emotion regulation protocols.

Study	Functional navigation (target areas)	Task	Emotions	Population	Emotional stimuli	NF sessions	ROI regulation	Training time effect	Transfer effect	Cogn./clin. effects vs. baseline (and CG)
Hamilton et al. (2016)	watching negative pictures (AI, OFC, dACC, IFG)	down	negative down	healthy subjects	Y	1	NR	NR	Y (CG ++)	Y (CG ++)
Johnston et al. (2010)	watching negative vs. neutral pictures (VLPFC, insula, MTL incl. amygdala)	up	unspec. up	healthy subjects	N	1	Y (no CG)	Y	NA	NR
Johnston et al. (2011)	watching positive vs. neutral pictures (VLPFC, insula, amygdala)	up	unspec. up	healthy subjects	N	1	Y (CG ++)	Y	NA	N
Li et al. (2016a)	MVPA of happy/sad mental imagery	up	unspec. up	healthy subjects	N	1	NR (no CG)	NR	NA	NA
Li et al. (2016b) [b]	MVPA of happy/sad mental imagery	up	positive up	healthy subjects	N	1	Y (CG ++)	Y	NA	N
Linden et al. (2012)	watching positive vs. neutral pictures (VLPFC, insula, DLPFC)	up	positive up	patients with depression	N	4	Y (CG outside scanner)	Y	NA	Y (CG ++)
Lorenzetti et al. (2018)	tenderness/anguish vs. neutral, 2 methods: 1. ROI: septo-hypothalamic area (tenderness), right amygdala (anguish); 2. SVM)	up	positive and negative up	healthy subjects	N	2	Y[c] (no CG)	NR	NA	Y
Mehler et al. (2018) [d]	watching positive vs. neutral pictures (limbic and frontal regions)	up	positive up	patients with depression	N	4	N (CG -)	N	N	Y (CG -)
Moll et al. (2014) [a]	SVM of tenderness and pride	up	positive up	healthy subjects	N	1	Y (CG ++)	Y	NA	N

Y = yes, N = no, NA = not assessed, NR = not reportedAI = anterior insula, CG = control group, clin. = clinical, cogn. = cognitive, contam. = contamination, dACC = dorsal anterior cingulate cortex, DLPFC = dorsolateral prefrontal cortex, IFG = inferior frontal gyrus, MTL = middle temporal lobe, MVPA = multivoxel pattern analysis, OCD = obsessive-compulsive disorder, OFC = orbitofrontal cortex, ROI = region of interest, SVM = support vector machine, unspec. = unspecific, VLPFC = ventrolateral prefrontal cortex.

[a] Yes based on average results per three runs; No based on the results from the last run.

[b] ROI regulation results are based on percentage of trials correctly classified by SVM classifier, taken as an indicator of successful engagement of ROI reflecting predefined emotional state.

[c] Results FWE corrected.

[d] Results FDR corrected.

One study also demonstrated successful ROI regulation in patients with depression with improvement in depression scores as compared to a control group.

4.1.6. Summary of brain targets and populations

In sum, the amygdala and AI were shown to be suitable targets for rt-fMRI-NF in healthy people and in several patient groups. Amygdala activity turned out to be a feasible target for upregulation by increasing positive emotions and for downregulation by decreasing negative emotions. In contrast, the feasibility of AI upregulation gained more empirical support than downregulation in healthy people, though one study showed positive outcomes for phobic patients (Zilverstand et al., 2015). Other regions related to emotional processing, such as the ACC, OFC, and dopaminergic reward-related regions, appear to be suitable for NF in emotion regulation as well. On the other hand, PFC regulation does not seem to be augmented by NF, at least in studies that presented NF from a predefined region. The presence of PFC NF can be associated with decreased activity in limbic regions and reduction in clinical symptoms. The feasibility of prefrontal regulation is more consistent in studies that used individual functional navigation of ROIs. Connectivity-based NF seems to be a promising path to NF emotion regulation training. Although the individual selection of target regions based on functional navigation has been shown to produce successful NF regulation in healthy people and patients with depression, this approach may have limitations for patient populations in general. It is possible that regions could not be detected by functional localizer tasks because these regions are not activated in the contrast due to functional impairment. In terms of patient populations suitable for NF, patients with depression, PTSD, OCD, contamination anxiety, spider phobia, BPD, and schizophrenia have been shown to be able to regulate the activity of various brain regions using NF presentation, though more studies with control groups are needed. Some studies have also shown improvement in clinical symptoms and potential for long-term clinical effect sustainability following NF training. Since many studies lack control groups and/or cognitive/clinical effect evaluation, the conclusions are rather preliminary and require further empirical testing and more conservative elaboration in the future (e.g., by a meta-analysis when enough data is generated).

4.2. Emotion regulation protocols

4.2.1. Upregulation tasks

All but one study instructing subjects to upregulate positive emotions presented no additional stimuli (Fig. 2). Another group of studies similarly did not present any additional stimuli but instructed the subjects to use either positive or negative mental strategies for upregulation (referred to as “unspecified upregulation”). The majority of these studies show positive results irrespective of brain targets and populations (see Table 3), although comparisons with control groups are absent in some studies. The relative lack of studies presenting additional stimuli and instructing subjects to upregulate emotions may stem from the task characteristic itself: if we want the subjects to learn to increase the intensity of their emotional experiences, it could be counterproductive to evoke emotions by presenting additional stimuli at the beginning of the

trial. In such designs, a possible ceiling effect could prevent subjects from further increasing their emotions. Another reason could be that most upregulation studies instruct subjects to use mental imagery for upregulation, which can potentially interfere with other visual stimuli.

On the other hand, Koush et al. (2017) showed that positive emotion upregulation using additional stimuli is possible. In this study, NF led to more successful PFC-limbic connectivity upregulation in subjects who were watching positive social situation pictures and their task was to imagine experiencing the scene. This study shows the potential for enhancing positive emotions associated with specific, e.g. socially desirable stimuli. In contrast, several studies used the upregulation of negative emotions with the presentation of additional stimuli. In contrast to the study by Paret et al. (2018), subjects in the study by Veit et al. (2012) were able to upregulate AI while watching threat pictures by imagining themselves being involved in the situation. The discrepancy in the results of the two studies is likely related to the different target regions. While upregulation of amygdala activity by increasing negative emotions during simultaneous presentation of negative stimuli is difficult because of the ceiling effect, upregulation of AI activity in the same situation could be more feasible because AI is involved not only in the processing of negative emotions, but also in the general NF control network (Emmert et al., 2016; Paret et al., 2018).

4.2.2. Downregulation tasks

All but one study focused on downregulating negative emotions presented emotion-evoking stimuli (see Fig. 2). The suitability of this approach, i.e. arousing emotions by external stimuli and the subsequent downregulation of the evoked emotions, is supported by successful brain target regulation in the majority of respective studies, irrespective of the target population and the nature of the emotional stimuli (see Table 3). The two studies that did not find regulation success compared to control conditions were from Veit et al. (2012) and Paret et al. (2018). As mentioned earlier, mixing downregulation and upregulation in these studies could have made the negative downregulation more difficult. However, the absence of control groups in most of these studies prevented the evaluation of NF-added value. The only study involving negative emotion downregulation without emotional stimuli used an approach in which the subjects were first instructed to upregulate negative emotions themselves using mental imagery and, subsequently, to downregulate those negative emotions (MacDuffie et al., 2018), but the results of the ROI downregulation were not reported in this study.

Downregulation of positive emotions has not been studied. Two out of four studies referred to in Fig. 2 and Table 2 as “unspecified downregulation” instructed subjects to decrease overall emotional experiences without presenting any additional stimuli; subjects were instructed specifically to relax or “turn off the engine” (Cohen Kadosh et al., 2016) or to imagine boring events (Greer et al., 2014). This approach could serve for more general, situation-unspecific training of relaxation or meditation that could be aided by fMRI-NF. However, existing studies do not provide sufficient support for the success of this approach due to a lack of control conditions and control groups. To be successful, this kind of neural regulation may require more training time, since the number of sessions in the current studies was limited. Another two studies exploring unspecified downregulation (Marxen et al., 2016; Weiskopf et al., 2003) did not provide the subjects with any instructions for regulation. Weiskopf et al. (2003) presented only single-subject data; the subjects in Marxen et al. (2016) did not downregulate ROI during the NF training as compared to the control condition, but they were successful in transfer runs.

In sum, the use of NF to upregulate either positive or negative emotions seems to be possible without presenting additional stimuli, though success depends on the target region. A few studies show the feasibility of upregulating emotions with a parallel presentation of emotion-evoking stimuli, though this task seems prone to failure. On the other hand, downregulation training seems to be more suitable with the use of stimuli to evoke emotions that can be consequently downregulated.

4.2.3. Ethical issues in emotion upregulation and downregulation

While upregulating positive emotions and downregulating negative emotions represent clearly desirable tasks from a clinical point of view, the upregulation of negative emotions and downregulation of positive emotions bring some ethical concerns. How could it be useful to promote negative emotions? In total, 10 studies included negative upregulation. The studies can be divided into three categories based on the purpose of the negative upregulation. Lorenzetti et al. (2018), Paret et al. (2018), Posse et al. (2003), and Veit et al. (2012) used negative upregulation training in healthy people from a basic science perspective, i.e. to examine the neural correlates of the negative emotion upregulation process. These studies contributed to the understanding of brain mechanisms of emotion regulation, NF control, and NF monitoring.

Two other studies used negative upregulation with the aim of promoting emotional awareness or empathy, specifically Sitaram et al. (2014) in sexual offenders and Yao et al. (2016) in healthy people. Emotional awareness, including awareness of both positive and negative emotions, is an important condition for adaptive emotion regulation (Gross and Jazaieri, 2014) and it is decreased in many psychiatric patient populations, such as patients with eating disorders (Westwood et al., 2017), schizophrenia (O'Driscoll et al., 2014), addiction (Morie et al., 2017), and somatization disorders (De Gucht and Heiser, 2003). Thus, negative upregulation as part of emotional awareness training could be theoretically beneficial in patient groups with reduced emotional awareness, but careful debriefing and clinical monitoring is needed to prevent any adverse effects on emotional wellbeing.

Finally, MacDuffie et al. (2018), Rance et al. (2018), Scheinost et al. (2013), and Scheinost et al. (2014) used negative upregulation together with negative downregulation as part of training to generally control the target brain area. Since all four studies demonstrated improvements in some cognitive or clinical outcomes in the experimental groups, such an approach could constitute a promising method of brain activity regulation learning, possibly by teaching the patients flexible neural control or by making the patients aware of the mental processes that promote symptom intensity.

Overall, using negative upregulation might be useful in some cases, but could be harmful in others. It is necessary to point out that rt-fMRI-NF has the potential to induce long-term changes that should be considered when implementing negative upregulation in NF designs. The question remains whether positive emotion downregulation, which has not yet been used in rt-fMRI-NF studies, could be also beneficial in some way. Although intentional reduction of positive emotions may sound clinically irrelevant or even inappropriate, it could theoretically be useful in patients who show exaggerated reactions to positive stimuli with possibly adverse consequences, such as patients with bipolar disorder (Keener et al., 2012) or with high positive urgency (Cyders and Smith, 2007).

4.3. Continuous vs. intermittent NF

Hellrung et al. (2018) directly compared success in amygdala upregulation between continuous and intermittent NF with a no NF control group. The authors conclude that intermittent presentation is superior to continuous presentation because continuous NF is more cognitively demanding. However, this factor did not lead to a difference in regulation success between the groups, suggesting that both methods of NF presentation (i.e., continuous and intermittent) may have their specific characteristics, but can be similarly effective. Regarding the hypothesis that intermittent NF may be more useful in studies with additional stimuli presentation due to the reduction of visual distractors, all studies that presented NF in the intermittent form also presented emotional stimuli (Buyukturkoglu et al., 2015; Hamilton et al., 2016; Koush et al., 2017; Posse et al., 2003; Sarkheil et al., 2015; Zilverstand et al., 2015). However, ROI regulation success seems to follow from different parameters than the choice of continuous or intermittent NF presentation in these studies. Specifically, ROI regulation was successful for all ROIs in these studies except the PFC regulation in Sarkheil et al. (2015) and

Zilverstand et al. (2015) and the results of Buyukturkoglu et al. (2015) are influenced by low statistical power. On the other hand, another group of studies that presented emotion-evoking stimuli used continuous NF (Brühl et al., 2014; Herwig et al., 2019; Nicholson et al., 2017; Paret et al., 2018, 2016a; 2014; Rance et al., 2018; Scheinost et al., 2014, 2013; Veit et al., 2012), but most of these studies did not use a control group or do not report regulation success or found differences only in down-regulation vs. upregulation blocks, not in comparison to a baseline control condition.

In sum, successful ROI regulation in studies with emotion evoking stimuli were reported in studies with both intermittent (Hamilton et al., 2016; Koush et al., 2013; Zilverstand et al., 2015) and continuous (Brühl et al., 2014; Herwig et al., 2019; Paret et al., 2016a, 2014) NF. However, there is currently not enough evidence to state whether the use of continuous or intermittent NF is superior in emotion regulation. More studies comparing both continuous and intermittent NF presentation are needed, especially studies with simultaneous emotional stimuli presentation.

4.4. Control groups

Some changes following the presentation of alternate ROI NF in control groups were found; however, the observed effects were more pronounced in the experimental groups. Specifically, healthy subjects in both the experimental and control groups in the study by Paret et al. (2014) were able to downregulate the amygdala, but the effect persisted in the transfer run only in the experimental group, and connectivity with the VMPFC only increased with amygdala NF (Paret et al., 2016b). Yuan et al. (2014) found altered amygdala connectivity in both the experimental and control groups in patients with depression; however, it was related to decreased depression symptoms only in the experimental group. Other studies found successful regulation and behavioral effects only in experimental groups (Hamilton et al., 2016; Lawrence et al., 2014; Misaki et al., 2018; Yao et al., 2016; Young et al., 2017b, 2014, Zotev et al., 2018, 2011). The only study with alternate ROI NF control group which found the same pattern of results in experimental and control groups is the study by Mehler et al. (2018); however, the study presents results only with FDR correction which probably makes the results underestimated in comparison to the majority of studies presenting uncorrected results.

Studies which used yoked NF in control groups generally did not find regulation success or cognitive/clinical effects in the control groups in healthy people (Hamilton et al., 2011; Koush et al., 2017), patients with depression (Hamilton et al., 2016), or patients with anxiety (Rance et al., 2018; Scheinost et al., 2013). From the studies with no NF control group, Zilverstand et al. (2015) found reduced anxiety after AI downregulation training in both the experimental and the control group, supporting the learning potential of the emotion regulation protocol itself; however, the effect was again more pronounced in the experimental group (regarding both AI downregulation and anxiety decrease). Other studies found successful NF regulation or cognitive/clinical effects only in experimental groups (Hellrung et al., 2018; Johnston et al., 2011; Li et al., 2016b; Moll et al., 2014; Sarkheil et al., 2015). Two studies provided a direct comparison of multiple control groups (Caria et al., 2010, 2007). In both studies, healthy people were instructed to upregulate AI and the regulation was successful only in the experimental group as compared to the no NF and alternate ROI NF control groups. However, samples in both studies are too small to draw further conclusions about the control group types.

In sum, regardless of control group type, most studies show some effects in experimental groups exclusively. Although some studies demonstrated either successful ROI regulation or cognitive/clinical effects in control groups, the results were usually more pronounced in experimental groups, demonstrating an additional effect of NF. First, it should be noted that at least some of the findings likely result from unplanned exploratory analyses. Therefore, the risk of false positives is increased and findings that have not yet been replicated should be interpreted with caution. Second, there is no evidence that yoked or alternate ROI NF would lead to worse performance or negative cognitive/clinical effects, with the exception of the study by Caria et al. (2010) in which the control group decreased activity in AI while their task was AI upregulation. Third, yoked NF could undermine learning emotion regulation by confusing the subjects, leading to an absence of changes in control groups. Compared to yoked NF, more effects in both regulation success and cognitive/clinical effects have been observed in control groups with alternate ROI NF of the subject's own brain. It is theoretically possible that subjects can partially profit from seeing this form of NF that still results from activity in their own brains. Fourth, only one study in which the control group used no NF found partial effects in the control group. However, learning can be undermined in such no NF groups because of the absence of blinding and the different motivational aspects between the experimental and control groups. More studies with sufficiently large samples and appropriate blinding are needed to directly compare outcomes with different control group types.

4.5. Emotion regulation instructions

Studies differ in the type of emotion regulation instructions (e.g., mental imagery or cognitive reappraisal; see Fig. 4), as well as in the level of instruction detail or previous training in emotion regulation strategies. For example, in studies instructing subjects to use emotional imagery, some authors performed interviews with the subjects before the experiment to facilitate emotion retrieval (Young et al., 2014; Yuan et al., 2014; Zotev et al., 2016, 2013, 2011) or instructed subjects to write down several specific memories before the experiment (Li et al., 2016b, 2016a; Zotev et al., 2014). Brühl et al. (2014) provided simple instructions for cognitive reappraisal; Sarkheil et al. (2015) and Zilverstand et al. (2015) provided subjects with previous training of cognitive reappraisal. Some studies provided only more general instructions (see in Fig. 4).

Based on the current literature, it is not possible to say whether it is more advantageous to provide subjects with specific strategies or even training, or rather to let the subjects to find their own strategies during the task. However, providing subjects with no information about the regulation task at all seems to create more difficult conditions, as demonstrated by the overall unsuccessful results in ROI regulation during three fMRI sessions in the study by Marxen et al. (2016). In some cases, providing specific instructions might be necessary to prevent the use of undesirable strategies. This is especially a concern for upregulation studies providing NF from brain targets such as the amygdala or AI, since their activity increases with emotional intensity irrespective of emotional valence. If no strategies or strategies for unspecific emotional imagination are provided, the subjects can increase ROI activity with both positive and negative emotions, which might not be desirable in some cases. For example, in patients with depression, it might be necessary to specify the need for employing positive emotion-evoking strategies; the undesirable use of negative emotion-evoking strategies for ROI upregulation might even be harmful.

4.6. Suggestions for results presentation in rt-fMRI-NF studies

As can be seen in Tables 3 and 4, studies differ in the parameters according to which they evaluate the success of NF training. Most studies present the results of several analyses; however, only a few take into account correction for multiple comparisons. Thus, there is an increased risk of false positives. On the other hand, some studies do not present the evaluation of ROI regulation results at all, making it impossible to evaluate the study in this respect based on the published information. Another problem is the frequent absence of control groups, which makes it impossible to conclude firmly whether NF led to the improvement of ROI regulation. In addition, as previously raised by Thibault et al. (2018),

experiment results are often overstated. For instance, significant ROI regulation found only in a small part of the NF training can be presented as overall successful ROI regulation. Some studies also describe statistical trends as positive results.

We believe that the quality of rt-fMRI-NF in emotion regulation can be significantly improved by establishing a consensus on which results should be reported and by preplanning the analysis accordingly. Based on this literature review, we have several recommendations for result presentation for forthcoming NF studies.

First, ROI activity regulation as compared to control conditions is one of the most fundamental results of such studies, and therefore it should be reported. Control conditions should be designed so that they are as close as possible to the experimental condition. For example, when comparing upregulation while watching emotional pictures with upregulation while watching neutral pictures or with resting, it is more likely to find successful ROI regulation with the emotional pictures. A more appropriate control condition could be watching similar emotional pictures without attempting regulation.

Second, if we suppose that NF induces learning of ROI regulation, the analyses of linear trends in ROI regulation should be presented. Furthermore, results should be reported for time blocks separately, or in addition to the average per session.

Third, if possible, control groups should be implemented in studies and the results of comparisons between experimental and control groups in all analyzed parameters should be reported.

Fourth, the consequences of NF training should be evaluated. This can be done in multiple ways. One way is implementing and analyzing transfer runs. Additionally, studies with patient samples should evaluate the clinical effects of NF training. If possible, it is appropriate to assess long-term clinical effects since some existing studies suggest that the NF training effects could be delayed.

It is worth noting that some studies demonstrate clinical benefits of NF training, although they did not find significant ROI regulation (e.g., Zotev et al., 2018) or they did not report relevant results (Hamilton et al., 2016; MacDuffie et al., 2018; Scheinost et al., 2013). It is possible that NF training can induce beneficial effects even though ROI regulation during NF training was not successful. This could be explained by short NF training (typically one session), low statistical power of the study (e.g., small sample), or correction for multiple comparisons (if it was applied). The consistent presentation of ROI regulation in the literature can aid future meta-analyses in resolving this issue.

5. Conclusion

Real-time fMRI neurofeedback (rt-fMRI-NF) is a promising tool for emotion regulation enhancement in some groups of patients with mental disorders associated with emotion regulation impairment. The strongest support for the beneficial effect of rt-fMRI-NF has been shown in increasing positive emotion experiencing in patients with depression and in decreasing anxiety in patients with anxiety disorders. Symptom reduction following NF training has been reported in patients with PTSD, BPD, and schizophrenia, but the absence of direct comparisons with control groups in these studies makes it impossible to evaluate the added value of NF.

The ability to aggregate results is limited because of the lack of standards for evaluating results. Future studies are well advised to adhere to widely accepted guidelines in reporting results, such as the guidelines outlined in the consensus paper preprint by Ros et al. (2019). The field will benefit from explicit differentiation of a priori and exploratory hypotheses, and of reporting of ROI regulation success. The use of control groups and assessments of clinical symptom changes following NF training in patient groups is also recommended.

Declaration of interests

None.

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4.3 Repetitive transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a safe method of non-invasive brain stimulation. A magnetic coil is placed above a participant's head at the desired location which induces a magnetic field reaching the brain about two centimeters from the coil. Electric pulses are induced to the brain tissue through electromagnetic induction. In repetitive transcranial magnetic stimulation (rTMS), a sequence of repeated pulses is delivered with the aim of cortical excitability and connectivity modulation. Although we can only reach cortical brain areas with rTMS, deeper brain structures can be affected through brain connectivity. Stimulation with different frequencies can be applied where low-frequency stimulation (< 1 Hz) is typically considered inhibitory and high-frequency stimulation is typically considered excitatory (> 5 Hz) (Lefaucheur, 2019), however, the brain modulatory effects of rTMS are probably more complicated in fact (Wang et al., 2020). The main indication of rTMS in mental disorders is in major depression for which is rTMS approved method of treatment by Food and Drug Administration and European Union (Ustohal, 2018). However, rTMS has been explored in other mental disorders including BPD. Theoretically, rTMS could increase prefrontal cortex excitability, and, subsequently, lead to improvements in emotion dysregulation and impulsivity.

4.3.1 rTMS in patients with borderline personality disorder

rTMS was used in patients with BPD in 12 studies with a total sample of 121 BPD patients (Arbabi, Hafizi, Ansari, & Ali, 2013; Cailhol et al., 2014; Calderón-Moctezuma et al., 2020; De Vidovich, Muffatti, & Caramia, 2016; Feffer et al., 2022; Feffer, Peters, Bhui, Giacobbe, & Downar, 2017; Gündoğmuş, Örnek, & Altınyay, 2018; Krisanaprakornkit, Paholpak, Tassaniyom, & Pimpanit, 2010; Reinsberg et al., 2023; Reyes-López et al., 2017; Tomas Svěrák et al., 2022; Tomáš Svěrák et al., 2019). Only three of these studies (44 total patients) were sham-controlled (Cailhol et al., 2014; Calderón-Moctezuma et al., 2020; Feffer et al., 2022) and no study was double-blinded. Most of the studies targeted various parts of the prefrontal cortex because it is hypothesized that high frequency rTMS can increase prefrontal excitability and, subsequently, prefrontal-limbic connectivity. These studies reported good tolerability of the treatment and various effects of rTMS in BPD patients, including improved self-control, emotion regulation, mood, anxiety, and executive functions.

Before our study (Svěrák, Linhartová et al., 2022; Annex 10), only one case report study (Arbabi et al., 2013) combined rTMS with neuroimaging, specifically fMRI. Although rTMS seems safe and potentially efficient for the treatment of BPD symptoms, we had no knowledge about the rTMS neural correlates and mechanisms. In our study (Svěrák, Linhartová et al., 2022; Annex 9), 14 patients with BPD underwent 15 sessions of high-frequency rTMS over the right DLPFC. Our goal was to target the inhibition network in the DLPFC area (using

individual neuronavigation based on the Go/NoGo task brain activity in fMRI) and subsequently strengthen its activity using high frequency rTMS in patients with BPD. We hypothesized that prefrontal rTMS will lead to improved BPD symptoms and enhanced DLPFC-amygdala connectivity.

The rTMS protocol led to decrease in impulsivity (as measured by UPPS-P self-reported questionnaire), emotion dysregulation (as measured by Difficulties in emotion regulation scale) and depression symptoms (measured by Montgomery and Åsberg Depression Rating Scale; Montgomery & Asberg, 1979). Regarding the neural effects, we did not observe any changes in prefrontal-amygdala connectivity. However, we observed decreased left-amygdala connectivity with nodes of posterior default mode network (pDMN; specifically, precuneus, posterior cingulate cortex and parietal lobules) after the rTMS treatment. Posterior part of DMN is associated with self-related and future-oriented reflection and emotional and attributional evaluation of situations (Cabanis et al., 2013; Xu, Yuan, & Lei, 2016). Previous studies reported increased involvement of pDMN in patients with BPD (Beblo et al., 2006; Doll et al., 2013) and increased connectivity of the amygdala with pDMN areas has been found to be associated with a number of negatively experienced phenomena such as depressive rumination, sleep deprivation complicated grief and high suicidal ideation (Chen, Ward, Claesges, Li, & Goveas, 2020; DeWitt, Aslan, & Filbey, 2014; Peters, Burkhouse, Feldhaus, Langenecker, & Jacobs, 2016; Shao et al., 2014).

Importantly, decreased amygdala connectivity with pDMN in resting state in our study was positively correlated with decreased depressive symptoms and with decreased lack of thinking before acting and planning (Lack of Premeditation from the UPPS-P scale). This means that the larger the decrease in amygdala-pDMN connectivity in the resting state after rTMS as compared to before rTMS, the greater the symptom improvement. Thus, decreasing amygdala-pDMN connectivity seems to be beneficial in patients with BPD and can be achieved by the prefrontal rTMS.

In sum, prefrontal rTMS seems to be safe and efficient in patients with BPD. Our study brought first evidence about potential brain mechanisms of prefrontal rTMS in BPD through reduction of amygdala-pDMN connectivity. Two main problems prevent us from concluding further evaluation of rTMS in BPD. First, there is a lack of placebo-controlled studies. Since rTMS can potentially induce a strong placebo effect, it is necessary to bring evidence on comparison of active and sham rTMS. Second, we have limited data about the rTMS effect duration. Thus, randomized placebo-controlled studies with effect duration measurements are needed. In 2023, we obtained a research grant for this purpose, and its results are currently in publication process.

Annex 10

Svěrák, T., **Linhartová, P.,** Gajdoš, M., Kuhn, M., Látalová, A., Lamoš, M., Ustohal, L., & Kašpárek, T. (2022). Brain connectivity and symptom changes after transcranial magnetic stimulation in patients with borderline personality disorder. *Frontiers in Psychiatry,* 12:770353. doi: 10.3389/fpsyt.2021.770353
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Brain Connectivity and Symptom Changes After Transcranial Magnetic Stimulation in Patients With Borderline Personality Disorder

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Objectives: Repetitive transcranial magnetic stimulation (rTMS) is an innovative method in the treatment of borderline personality disorder (BPD). We hypothesized that prefrontal rTMS in patients with BPD leads to improved BPD symptoms and that these effects are associated with brain connectivity changes.

Methods: Fourteen patients with BPD received 15 sessions of individually navigated prefrontal rTMS over the right dorsolateral prefrontal cortex. Clinical effects were measured by the Borderline Symptom List 23, UPPS-P, the Difficulties in Emotion Regulation Scale (DERS), the Zung Self-Rating Anxiety Scale (SAS), and the Montgomery and Åsberg Depression Rating Scale (MADRS). Effects of rTMS on brain connectivity were observed with a seed correlation analysis on resting-state fMRI and with a beta series correlation analysis on Go/No Go tasks during fMRI. Assessments were made before and immediately after the treatment.

Results: The assessments after rTMS showed significant reductions in two subscales of UPPS-P, and in DERS, SAS, and MADRS. The brain connectivity analysis revealed significant decreases in amygdala and insula connectivity with nodes of the posterior default mode network (pDMN; precuneus, posterior cingulate cortex, parietal lobules). Connectivity changes were observed both in the resting state and during inhibition. The decrease of amygdala-pDMN connectivity was positively correlated with reduced depression and lack of premeditation after rTMS.

Conclusions: Despite the study limitations (open single-arm study in a small sample), our findings suggest a possible neural mechanism of rTMS effect in BPD, reduced amygdala connectivity with the pDMN network, which was positively associated with symptom reduction.

Keywords: transcranial magnetic stimulation, borderline personality disorder, connectivity changes, Go/NoGo task, posterior default mode network

INTRODUCTION

Borderline personality disorder (BPD) is a serious mental disorder characterized by instability of affect, self-image, and relationships, and by marked impulsivity including self-harm and recurrent suicidal behavior (1). Treatment of BPD is challenging. The primary treatment for BPD is psychotherapy, especially targeted approaches such as dialectical behavior therapy, schema therapy, mentalization-based treatment, and transference-focused therapy (2). Pharmacotherapy is only targeted at symptoms and is not recommended for the treatment of BPD unless targeting specific comorbidities (3, 4). Therapy dropout rates for BPD patients are typically high (5), and the development of new treatment methods for this life-threatening mental disorder is greatly needed.

On the neural level, BPD patients show impairment in multiple networks. Patients with BPD have been reported to show increased involvement of the posterior default mode network (6, 7) and increased connectivity of the anterior cingulate cortex with the amygdala and insula (8). While processing emotional stimuli, patients with BPD show increased and prolonged reactivity of the amygdala, altered prefrontal cortex responses, including the dorsolateral prefrontal cortex (DLPFC), and reduced connectivity between limbic and prefrontal regions as compared to healthy controls in functional magnetic resonance imaging (fMRI) studies (9–12). Reduced gray matter volume was found in BPD patients in the amygdala, insula, and DLPFC (13). Impaired prefrontal-limbic connections are typically described as a mechanism of impaired top-down emotional control in BPD, leading to increased impulsivity and impaired emotion regulation.

Repetitive transcranial magnetic stimulation (TMS, rTMS) is a potentially innovative method in the treatment of BPD. rTMS was used in patients with BPD in nine studies with a total sample of 72 BPD patients (14–22); two of those studies (24 total patients) were placebo-controlled studies (16, 22). Most of the studies targeted the prefrontal cortex because it is hypothesized that high frequency rTMS can increase prefrontal excitability and, subsequently, prefrontal-limbic connectivity. These studies reported good tolerability of the treatment and various effects of rTMS in BPD patients, including improved self-control, emotion regulation, mood, anxiety, and executive functions (23). Only one single case study (15) combined rTMS with neuroimaging, specifically fMRI. Thus, rTMS seems safe and efficient for the treatment of BPD symptoms, but knowledge of the rTMS neural correlate effects is missing and there are no data supporting the hypothesis that prefrontal rTMS leads to increased prefrontal-limbic connectivity.

In this study, patients with BPD underwent high-frequency rTMS of the right DLPFC (rDLPFC). High-frequency rTMS leads to increased cortex excitability, and patients with BPD have been found to have decreased activation predominantly in right DLPFC as compared to healthy controls (11). Also, Swick et al. (24) observed Go/NoGo (GNG) task activation as generally more right sided and DLPFC as connected with attentional executive control or top-down cognitive control and behavioral inhibition. Our goal was to individually target the inhibition network in the DLPFC area (based on the Go/NoGo task) and subsequently strengthen its activity using high-frequency rTMS in patients with BPD.

We hypothesized that prefrontal rTMS in patients with BPD can lead to improved symptoms, specifically to enhanced impulse control and emotion regulation and, based on previous studies, to decreased anxiety and depression. We hypothesized that these effects are associated with brain connectivity changes induced by prefrontal rTMS. We focused on exploring changes in brain connectivity in three regions of interest: the DLPFC, a brain area crucial for emotion and impulse regulation (25, 26) and a stimulation target in this study; the amygdala, a brain area associated with emotion experiencing intensity that is hyperactive in patients with BPD (9); and the insula, a crucial node in the inhibition network (24) and a brain area associated with experiencing negative emotions (27).To maximize the possibility of rTMS enhancing self-control and decreasing impulsivity, we chose individual neuronavigation of the rTMS target based on the fMRI results of a Go/NoGo task. GNG tasks are the most frequent test for measuring waiting impulsivity (28).

METHODS

Subjects

Fourteen patients with BPD (3 men; age: $M = 23.57$, $SD = 4.73$ years) underwent a prefrontal rTMS protocol. The inclusion criteria were: 5 out of 9 criteria for BPD according to DSM-5 (1), age between 20 and 45, and stable medication for at least 6 weeks before the stimulation and until the end of the stimulation. The exclusion criteria were addiction (except nicotine), bipolar I disorder, and major depressive disorder (current or in the history of the patient), current acute psychotic state, a schizophrenia-spectrum disorder, and contraindications preventing MRI or rTMS.

Scales and Questionnaires

Self-reported measures were included to assess the clinical effect of the treatment in areas that were hypothesized as possibly improvable by rTMS. Borderline symptoms were measured by the Borderline Symptom List 23 (BSL-23), an established measure for BPD symptom severity (29). Impulsivity was measured by the UPPS-P scale (30, 31), specifically the subscales Lack of Premeditation, Lack of Perseverance, Negative Urgency, and Positive Urgency. Sensation Seeking was left out since it does not seem to be altered in BPD (32). Emotion regulation was measured by the Difficulties in Emotion Regulation Scale [DERS; (33)], and anxiety was measured by the Zung Self-Rating Anxiety Scale [SAS; (34)]. Depression symptoms were measured by the Montgomery and Åsberg Depression Rating Scale [MADRS; (35)] assessed by a clinical psychologist who did not participate in the rTMS patients treatment. The questionnaires were administered to the patients before and after the stimulation protocol. Possible side effects of rTMS were evaluated by research staff before and after each stimulation session, based on the recommendations of McClintock et al. (36).

Magnetic Resonance Imaging

Functional MRI was done immediately before and after the rTMS protocol with 3T Magnetom Siemens Prisma machine (Siemens Healthcare GmbH, Erlangen, Germany) at the Central European Institute of Technology (CEITEC) in Brno, Czech Republic. The acquisition sequence was three-dimensional magnetization-prepared rapid gradient echo [3D inversion recovery; anatomical T1; 3D MP-RAGE; Repetition time (TR) = 2,300 ms, Echo time (TE) = 2.33 ms, voxel size = 1 × 1 × 1 mm^3, FoV (224 × 224 mm), Flip Angle (FA) = 8°, 240 sagittal slices]. We used a gradient-echo echoplanar-imaging sequence sensitive to BOLD contrast for acquisition of one task-free and four task fMRI sessions (GNG task) with the following task-free/task parameters: TR = 750/2,280 ms, TE = 35 ms, voxel size = 3 × 3 × 3 mm^3, FoV (192 × 192 mm), FA = 46°/75°, multiband factor = 4/1, 39/40 transversal slices, 380/153 scans.

Go/NoGo Task

We adapted the GNG task according to the task design from Albares et al. (37). In the beginning of each trial, a variable duration fixation cross was presented for 2–6 s, followed by a Go or NoGo stimulus lasting 0.2 s, and finally followed by a post-trial black screen for 2 s. We used white letters A and B on a black background as the Go and NoGo stimuli. The fixation cross was green in 1/3 of cases and red in 2/3 s of cases. The patients were instructed that a Go or NoGo stimulus can appear after the red cross, while only the Go stimulus can appear after the green cross (Go condition, NoGo condition, and Go-control condition; **Figure 1**). The ratio of Go and NoGo stimuli occurring after the red cross was equal. The patients were further instructed to press a button as quickly as possible when a Go stimulus appeared, but not to press the button when a NoGo stimulus appeared (i.e., to perform inhibition). The task contained 4 blocks of 54 trials each with breaks between the blocks; the whole task lasted ∼25 min. NoGo vs. Go contrast was used to analyze the neural correlates of inhibition.

Individual Neuronavigation

The rDLPFC was targeted individually by stereotactic neuronavigation (software Brainsight, v. 2.02), fMRI data analysis for neuronavigation was performed in SPM12. The rDLPFC anatomical mask was derived from the Destrieux neuroanatomic atlas (38) from FreeSurfer software (39) as a conjunction of the sulcus frontalis inferior, sulcus frontalis medius, and gyrus frontalis medius. Regions of interests were further specified by creating a sphere mask with radius 15 mm around the maximum in rDLPFC derived for the contrast between NoGo and Go conditions and by generating the mask for an area up to 20 mm under the skull. Within the brain area defined by combining those masks, the point of individual peak BOLD signal in the contrast between NoGo and Go conditions was used as rTMS target.

rTMS

We used the DuoMAG XT magnetic stimulator (Deymed Diagnostic) with a 70BF air-cooled coil. The patients underwent 15 stimulation sessions at 110% of their individual resting motor threshold (RMT) over a period of 3 weeks with one session each working day. One stimulation session contained 1,500 pulses (total 22,500 pulses during the whole procedure) divided into 10 trains with 10 Hz frequency (train interval lasted 10 s, inter-train interval lasted 30 s). The RMT was measured before the first stimulation session and defined according to the Rossini-Rothwell method (40).

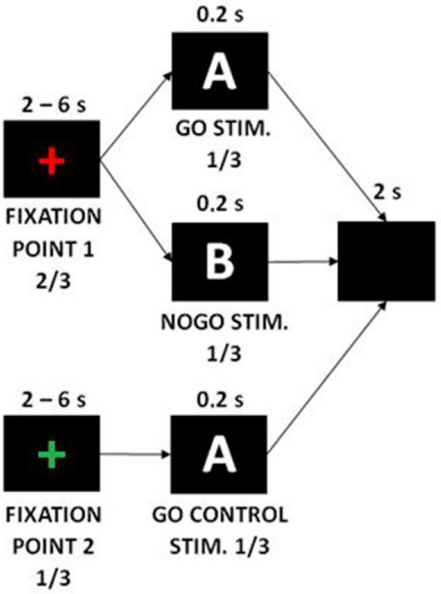

FIGURE 1 | Go/NoGo task design.

Statistical Analysis

Behavioral and self-reported data analysis was performed in jamovi software v1.6 (41). Differences before and after the rTMS treatment in self-report questionnaires and MADRS scores and in the relative frequency of mistakes after NoGo stimuli in the GNG task (NoGo errors) were analyzed by paired *t*-tests and non-parametric Wilcoxon rank test due to small sample size.

fMRI Analysis

fMRI Data Pre-processing

All functional datasets were preprocessed in SPM12 software (42) running under MATLAB 9.6 (Mathworks Inc., USA) with realign and unwarp, spatial normalization, and spatial smoothing (Gaussian filter with a full width at half-maximum of 6 mm). Task sessions were slice timing corrected before spatial normalization due to longer TR. The data were controlled for spatial abnormalities using the mask_explorer tool (43). We used framewise displacement (FD) criterion (44) to control for excessive movement and excluded all sessions where FD exceeded 0.5 mm in more than 20% of scans (one task-free and two task sessions were excluded).

Beta Series Correlation Analysis

We employed beta series correlation analysis (BSCA) (45) to investigate connectivity during distinct stages of the GNG

TABLE 1 | Self-reported differences before and after rTMS (paired *t*-test and Wilcoxon rank-test).

Measure		N	M	SD	t (df)	p	d
					W	p	r_{rb}
BSL-23	Before	14	43.29	22.28	1.562 (13)	0.142	0.417
	After	14	33.64	19.68	78.000	0.116	0.486
UPPSP-PRE	Before	14	30.29	3.99	**3.095 (13)**	**0.009**	**0.827**
	After	14	27.36	5.64	**91.000**	**0.017**	**0.733**
UPPSP-PER	Before	14	28.79	4.90	**2.692 (13)**	**0.018**	**0.720**
	After	14	25.14	4.80	**79.500**	**0.019**	**0.747**
UPPSP-NU	Before	14	37.14	5.60	1.158 (13)	0.268	0.310
	After	14	34.86	7.33	54.500	0.551	0.198
UPPSP-PU	Before	14	38.14	10.32	1.232 (13)	0.240	0.329
	After	14	35.07	8.09	51.000	0.366	0.308
DERS	Before	14	121.79	20.42	**3.345 (13)**	**0.005**	**0.894**
	After	14	101.29	27.75	**97.500**	**0.005**	**0.857**
SAS	Before	14	48.79	10.33	**2.178 (13)**	**0.048**	**0.582**
	After	14	43.14	11.64	82.500	0.064	0.571
MADRS	Before	14	14.79	5.94	**2.701 (13)**	**0.018**	**0.722**
	After	14	10.86	7.24	**81.000**	**0.014**	**0.780**
NoGo errors %	Before	14	0.12	0.12	0.756 (13)	0.463	0.202
	After	14	0.10	0.09	58.500	0.729	0.114

BSL-23, Borderline Symptom List 23; UPPSP-PRE, Lack of Premeditation; UPPSP-PER, Lack of Perseverance; UPPSP-NU, Negative Urgency; UPPSP-PU, Positive Urgency; DERS, Difficulties in Emotion Regulation Scale; SAS, Zung Self-Rating Anxiety Scale; MADRS, Montgomery and Åsberg Depression Rating Scale. Bold values meant statistic significant values.

task from selected seeds: left and right amygdala and left and right insula from AAL atlas (46) and rDLPFC from the Human Connectome Project multi-modal parcellation atlas (47). We added 12 movement regressors and white matter (WM) and cerebrospinal fluid (CSF) signals as confounders in the model. In the next step, we correlated the seed beta series (average from the ROI) representing the effects of regressors separately for NoGo and Go trials. To obtain the NoGo vs. Go contrast, we subtracted the connectivity maps for the mentioned conditions. We followed with the paired tests in SPM to identify the connectivity changes before and after rTMS stimulation. Reported group results are based on cluster-level inference at p (FWE) < 0.05 with an initial cut-off of $p < 0.001$.

Seed Correlation Analysis

We used seed correlation analysis (SCA) to analyze connectivity in task-free data with identical seeds as used for BSCA. Before SCA, we filtered low-frequency drifts using high-pass with a cutoff of 1/128 Hz. We also filtered the confounder signals from WM and CSF and the effect of 24 movement regressors. A paired t-test was used to assess the stimulation effects. Group results were corrected for multiple testing with cluster-level inference at p (FWE) < 0.05 with an initial cut-off of $p < 0.001$.

Association of Brain Connectivity and Symptom Change

To see whether the observed changes in brain connectivity were associated with changes in the scales measuring BPD symptoms, we performed Spearman correlations between the changes in brain connectivity (T2-T1) and changes in symptom measures (T2-T1; selected measures that showed significant decreases after the rTMS treatment). A positive correlation means that the higher the decrease of brain connectivity, the higher the decrease in measured symptom. A negative correlation means that the higher the decrease of brain connectivity, the lower the decrease in measured symptom. The results were not corrected for multiple comparisons due to the exploratory nature of this analysis and the small sample size.

RESULTS

RTMS was well-tolerated without any major side effects. Four patients reported headache after the stimulation, usually at the beginning of our protocol, which disappeared spontaneously without any medication after a short time.

Self-Reported Results

According to the self-reported measures (**Table 1**), rTMS led to significant reduction in Lack of Premeditation and Lack of Perseverance in the UPPS-P impulsivity scale, improvement in emotion regulation (DERS), reduction of depressive symptoms (MADRS), and borderline significant reduction of anxiety symptoms (SAS). There was no significant change in BSL-23, negative urgency and positive urgency, and no significant change in the percentage of NoGo errors in the GNG task after vs. before the treatment. Parametric and non-parametric tests yielded similar results.

fMRI Results

In the resting state after rTMS vs. before rTMS, we found a decrease in connectivity of the left amygdala with a cluster

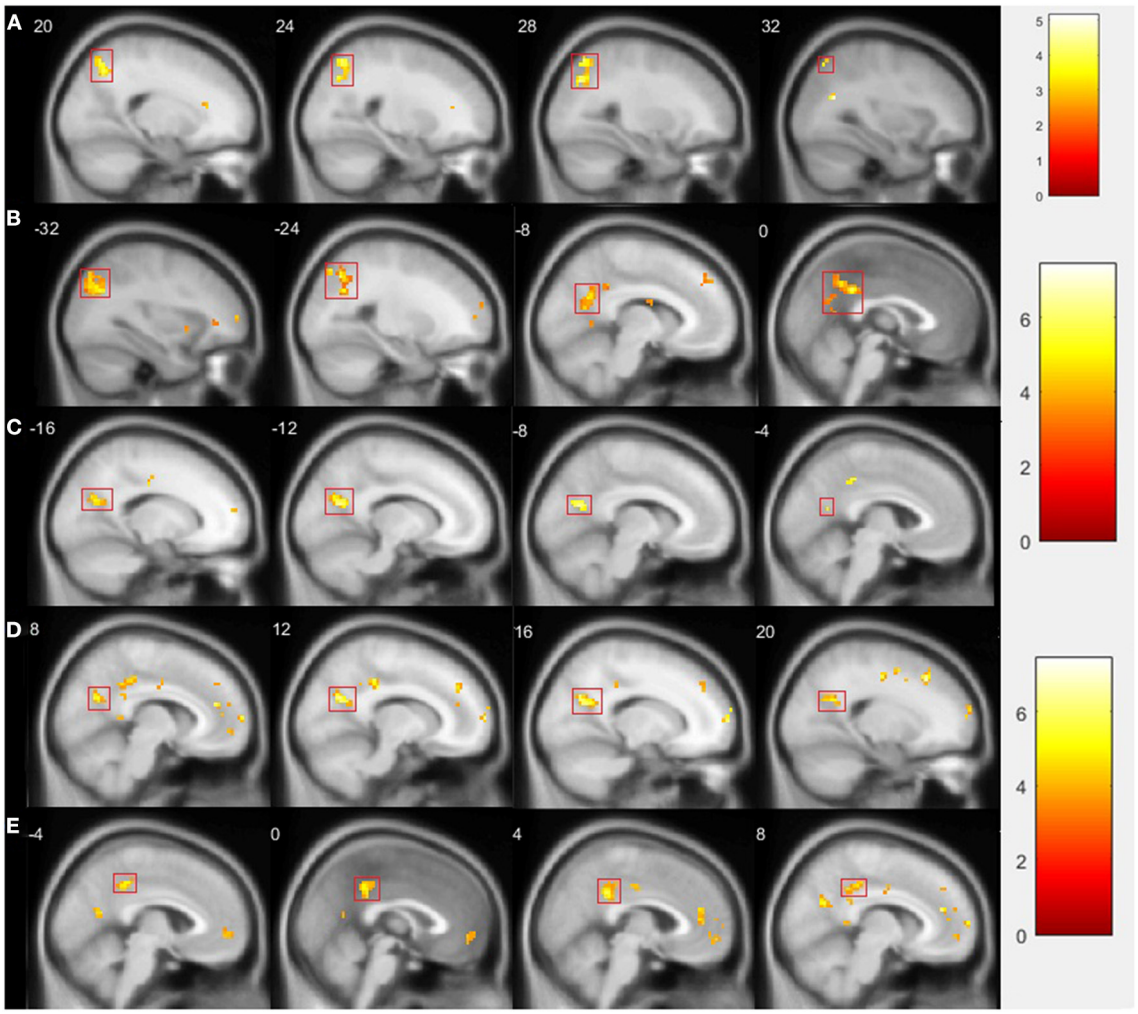

FIGURE 2 | Comparison of fMRI results after vs. before rTMS. Statistically significant changes are marked by a red rectangle ($p < 0.05$ FWE corrected on cluster level). **(A)** Presents decreased connectivity of left amygdala with cluster comprising right precuneus and superior parietal lobule during resting state; **(B)** shows decreased connectivity of left amygdala with cluster comprising left parietal lobule, precuneus, and middle and posterior parts of cingulate gyrus during GNG; **(C)** presents decreased connectivity of left insula with left precuneus during GNG; **(D)** shows decreased connectivity of left insula with right precuneus; **(E)** presents decreased connectivity of left insula with posterior cingulate gyrus.

comprising the right precuneus and superior parietal lobule [peak 27 −70 37 ($t = 5.00$, $p = 0.025$), 78 voxels; **Figure 2A**]. No significant changes in the right amygdala, insula, or right DLPFC connectivity were observed.

In the GNG task, specifically in the NoGo vs. Go contrast and after vs. before rTMS, we found decreased connectivity of the left amygdala with a cluster comprising the left parietal lobule, precuneus, and middle and posterior parts of cingulate gyrus [peak −15 −67 13 ($t = 5.99$, $p = 0.000$), 374 voxels; **Figure 2B**]; and a decrease in the connectivity of the left insula with the left precuneus [peak −9 −67 19 ($t = 5.96$, $p = 0.017$), 67 voxels; **Figure 2C**], with the right precuneus [peak 12 −64 25 ($t = 5.41$, $p = 0.014$), 70 voxels; **Figure 2D**], and with the posterior cingulate gyrus [peak 6 −40 28 ($t = 5.11$, $p = 0.010$), 74 voxels; **Figure 2E**]. No significant changes in the right amygdala, right insula, or right DLPFC connectivity were observed.

Association Between Connectivity and Symptom Change

We observed two trend associations of connectivity change and symptom change (**Table 2**). Decreased connectivity in the left amygdala with a cluster comprising the right precuneus and right superior parietal lobule in the resting state was positively correlated with decreased depression symptoms (MADRS; $r_s = 0.52$, $p = 0.067$) and Lack of Premeditation (UPPSP-PRE; $r_s = 0.53$, $p = 0.064$). We observed another negative correlation of decreased Lack of Perseverance (UPPSP-PER; $r_s = -.49$, $p = 0.076$) and decreased left insula connectivity with the right precuneus in the inhibition condition.

TABLE 2 | Spearman correlations of brain connectivity change with symptom measures change.

Resting state connectivity change seeds (T2-T1)		Scale change	Spearman *r* (*p*)
L amygdala	27 −70 37 (R precuneus, R sup. PL)	DERS	0.41 (0.162)
		MADRS	**0.52 (0.067)**
		SAS	−0.15 (0.635)
		UPPSP-PER	0.06 (0.837)
		UPPSP-PRE	**0.53 (0.064)**
Go/NoGo Task (NoGo vs. Go contrast) connectivity change			
L amygdala	−15 −67 13 (L precuneus, mid.-post. CC, L PL)	DERS	−0.27 (0.350)
		MADRS	0.13 (0.657)
		SAS	0.12 (0.691)
		UPPSP-PER	−0.36 (0.213)
		UPPSP-PRE	−0.25 (0.388)
L insula	−9 −67 19 (L precuneus)	DERS	−0.04 (0.887)
		MADRS	0.25 (0.381)
		SAS	−0.13 (0.647)
		UPPSP-PER	−0.13 (0.647)
		UPPSP-PRE	0.23 (0.432)
L insula	12 −64 25 (R precuneus)	DERS	−0.24 (0.401)
		MADRS	0.03 (0.928)
		SAS	−0.30 (0.306)
		UPPSP-PER	**−0.49 (0.076)**
		UPPSP-PRE	0.12 (0.678)
L insula	6 −40 28 (post. CC)	DERS	0.28 (0.326)
		MADRS	0.34 (0.240)
		SAS	0.04 (0.893)
		UPPSP-PER	0.15 (0.620)
		UPPSP-PRE	0.08 (0.780)

Correlation indicates association between brain connectivity decrease and symptom decrease. R, right; L, left; PL, parietal lobule; CC, cingulate cortex; DERS, Difficulties in Emotion Regulation Scale; MADRS, Montgomery and Åsberg Depression Rating Scale; SAS, Zung Self-Rating Anxiety Scale; UPPSP-PER, Lack of Perseverance; UPPSP-PRE, Lack of Premeditation. Bold values are trend associations of connectivity change.

DISCUSSION

This is the first study reporting both behavioral and neural effects of prefrontal rTMS in a sample of patients with BPD. We used high-frequency stimulation of rDLPFC based on the literature about fronto-limbic dysfunction in BPD (i.e., reduced fronto-cingulate activity leading to limbic hyperactivity) which underlies affective dysregulation and impulsivity (9, 11, 48).

Behavioral Effects

Regarding the performance in inhibition in the GNG task, the number of NoGo errors was low both before and after rTMS, and it did not significantly change. A small number of mistakes is normal in equiprobable tasks such as the one used in our study (28, 49). Regarding the self-reported results, we observed some improvement in all measured variables after the rTMS protocol. The improvement reached statistical significance in emotion regulation (DERS), depression (MADRS), and two UPPS-P impulsivity subscales—Lack of Premeditation and Lack of Perseverance (in other words, the abilities to think before acting and to persist in activities and decisions) and borderline significance in anxiety (SAS). High effects sizes were observed for the changes in Lack of Premeditation and emotion dysregulation, medium effect sizes were observed for changes in Lack of Perseverance and in anxiety and depression levels. The results are consistent with previous studies, specifically the decreased anxiety (19, 22), depression (14, 15, 18–20, 22), impulsivity (15, 19, 20) and affective instability (16). Overall, rTMS treatment had positive effects on some BPD symptoms including anxiety, depression, emotion dysregulation, and impulsivity. Interestingly, only one study (16) used high-frequency stimulation of the right DLPFC such as in our study; other studies used low-frequency stimulation of the same area (19), or high-frequency stimulation of the left DLPFC (14, 15, 19, 20), or DMPFC stimulation (18, 22). Our results are consistent across the previous studies (23). At least two interpretations might be considered here: either the clinical effects are caused by factors other than active stimulation, which might indicate a placebo effect, or the parameters of the stimulation protocol might not play a crucial role in the results, and the rTMS might instead act as a more global prefrontal intervention (thanks to cortico-cortical connections).

Neural Effects

In both the resting state and inhibition conditions, we found decreased left amygdala connectivity with the precuneus (PCN),

posterior cingulate cortex (PCC), and parietal lobules (PL) after rTMS. These regions are parts of the posterior default mode network (pDMN), which is associated with self-related (personal) and future-oriented reflection and thinking and emotional and attributional evaluation of situations (50, 51).

Previous studies reported increased involvement of pDMN in patients with BPD as compared to healthy controls, suggesting higher self-referential thinking (6, 7). Increased connectivity of the amygdala with pDMN areas has been found to be associated with a number of negatively experienced phenomena, such as depressive rumination [PCC (52)], sleep deprivation [PCC, PCN (53)], complicated grief [PCN (54)], and also history of abuse [PCC, PCN (55)] or risk-taking [PCC, PCN (56)]. Increased connectivity of the amygdala with PCN has been also identified in adolescents who attempted suicide or had high suicidal ideation as compared to adolescents with low suicidal ideation and healthy controls (57).

Importantly, decreased amygdala connectivity with pDMN (in resting state only) was positively correlated with decreased depressive symptoms and with decreased lack of thinking before acting and planning (Lack of Premeditation). This means that the larger the decrease in amygdala-pDMN connectivity in the resting state after rTMS as compared to before rTMS, the greater the improvement in depressive symptoms and premeditation ability. Thus, our results are consistent with previous literature reporting positive associations of amygdala-pDMN connectivity and borderline or depressive symptoms. Decreasing amygdala-pDMN connectivity seems to be beneficial in patients with BPD and was achieved after the prefrontal rTMS protocol in our study.

In the inhibition condition, we found decreased connectivity of the PCN and PCC with the left insula after rTMS as compared to before rTMS. Again, there was a decrease of pDMN areas connectivity. The insula processes interoceptive information to engage externally oriented attention and internal cognitive control, helps with integrating information from the limbic system, and is a major part of the inhibition network (24, 58, 59). The PCC, PCN, and insula have been found to be associated with an increased sense of personal agency, with the insula correlating specifically with personal agency in negative situations (50). Higher interconnectedness in the PCN and insula has been found in people with a history of childhood maltreatment (60). In another study, increased connectivity of the insula and PCN distinguished posttraumatic stress disorder patients with and without dissociation symptoms (61). The pDMN has been found to be deactivated during pain, while the insula is activated by pain (62). Increased pDMN-insula connectivity has been reported in patients with BPD during pain processing (63); while decreased pDMN-insula connectivity has been observed in healthy people (64), which might reflect a disturbance in pain processing in BPD and suggest more self-referential experiencing of pain in BPD (63).

In our study, we found a negative correlation of decreased insula-pDMN connectivity in the inhibition condition and symptom reduction—specifically with reduced Lack of Perseverance. Though previous studies suggest that decreasing insula-pDMN connectivity could be beneficial in patients with BPD, our data did not support the hypothesis that reduction in this connectivity is positively associated with symptom changes in patients with BPD. Moreover, it should be noted that we found the decrease of pDMN-insula connectivity only in inhibition condition and not in resting state. Thus, the effect might be more situation specific or task related than general, while previous studies usually report increased pDMN-insula connectivity in resting state or during pain processing.

Overall, previous studies suggest that increased connectivity of pDMN with the amygdala and insula is associated with increased self-referential and self-attributional thinking, especially in negatively perceived situations. These connectivity increases are then associated with symptoms commonly associated with BPD, such as depressive mood, risk-taking, and suicidality with pDMN-amygdala connectivity, and dissociation and disturbed pain processing with pDMN-insula connectivity. Increased connectivity in both cases have been linked to adverse experiences in childhood. Our study reported decreased pDMN-amygdala and pDMN-insula connectivity and decreased BPD symptoms. We observed decreased pDMN-amygdala connectivity both in the resting state and during an inhibition task. This result suggests that negative self-referential thinking was decreased during resting and during a task activity focused on impulse control. We found that symptom reduction was positively correlated with decreased amygdala-pDMN connectivity, but negatively correlated with insula-pDMN connectivity. Thus, the reduction of negative self-referential thinking associated with reduced pDMN connectivity with the amygdala seems to be a beneficial effect for patients with BPD and a candidate mechanism of the rTMS effect in patients with BPD.

In contrast to our initial hypothesis, we did not find any changes in the connectivity of the dorsolateral prefrontal area stimulated by rTMS. Thus, the mechanism of how prefrontal stimulation led to the connectivity and symptom changes observed in this study remains unclear. However, changes in DMN connectivity after high-frequency prefrontal stimulation were found in previous studies in healthy volunteers and in patients with depression and PTSD (65–67). Another study examining the neural effects of high-frequency DLPFC stimulation in 60 healthy people found no changes in DMN connectivity, but multiple increases in the connectivity of the cingulate and frontoparietal areas (68); this was not observed in our study. Several possible interpretations might be drawn concerning how prefrontal stimulation can induce distant connectivity changes without influencing the stimulation area connectivity *per se*. First, it is possible that the effects are induced by factors other than the intervention, including a placebo effect. Double-blind sham-controlled studies are needed to shed more light on this possibility. Second, prefrontal rTMS might actually induce distant beneficial brain changes, which would correspond with the hypothesis that the precise stimulation site might not be a crucial parameter at all. Third, it is possible that the current study did not have sufficient power to show prefrontal connectivity changes, and replication on a higher sample is needed. Moreover, medication in patients with BPD might influence the results since limbic hyperactivity has been found to be moderated by medication status in BPD patients (11).

Overall, no existing data currently support the hypothesis that prefrontal rTMS leads to symptom reduction by increasing the prefrontal-limbic connectivity, but symptom reduction might be achieved by prefrontal rTMS through distant brain connectivity changes, such as the decrease of pDMN-amygdala connectivity observed in this study.

Limitations

The major limitation of our study is the small sample size and absence of a control group. The placebo effect is usually relatively high in rTMS studies (69), and there is a risk that this study was influenced as discussed above. On the other hand, this is the first study to report the neural effects of rTMS in BPD patients. Our results should be taken as exploratory and hypotheses-generating; they should be verified in a placebo-controlled study.

Another possible limit is the choice of behavioral paradigm for individual neuronavigation. We chose this task to identify a DLPFC target most strongly related to impulse control within the aim to reduce impulsivity. However, patients with BPD typically show impulsive behavior under the influence of emotions (32, 70, 71). A different task activating inhibition under emotions or emotion regulation could be more appropriate for targeting rTMS in patients with BPD. On the other hand, given the existing studies of rTMS in BPD, the rTMS target does not seem to play any crucial role in achieving symptom improvement. We only observed changes in connectivity from the right DLPFC, but we did not analyze changes in connectivity within the whole prefrontal cortex. This could be also the reason we observed only distant changes in brain connectivity.

CONCLUSION

This study reports on behavioral and neural effects of high-frequency prefrontal rTMS in patients with BPD. After the stimulation protocol, we observed reduced emotion dysregulation, impulsivity, anxiety, and depressive symptoms. On the neural level, we identified decreased connectivity of the posterior default mode network areas with the amygdala and insula; this might reflect decreased negative self-referential thinking. Reduced amygdala-pDMN connectivity is a candidate mechanism of an rTMS effect in patients with BPD. Sham-controlled studies examining the effect of brain target and stimulation parameters for rTMS are needed.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, Tomas Sverak, upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Commission of University Hospital Brno Jihlavská 20, CZ - 625 00 BRNO. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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5 Future directions in BPD research and treatment

Despite substantial advances in our understanding and treatment of borderline personality disorder (BPD), several important challenges remain. Future research should focus on identifying the mechanisms through which effective treatments exert their effects, including the roles of emotion regulation, interpersonal functioning, self-concept, cognitive processes, and their neural correlates. Better understanding of these mechanisms may enable the development of more personalized interventions and improve treatment outcomes. Another major challenge is the limited availability of evidence-based treatments for BPD in Czechia. Given the increasing demand for specialized care, future research should investigate ways to enhance treatment accessibility and efficiency, including methods that can augment psychotherapy. In this regard, innovative approaches such as non-invasive brain stimulation and neurofeedback represent promising avenues for further investigation. Ultimately, the goal of future research should be not only to improve our understanding of BPD but also to translate scientific findings into effective, accessible, and individualized treatments that meaningfully improve patients' lives and reduce the burden of the disorder on patients, families, and healthcare systems.

6 Conclusion

Borderline personality disorder is a severe and life-threatening mental disorder characterized by pervasive emotion dysregulation, behavioral instability, and significant impairment in interpersonal and psychosocial functioning. The findings summarized in this habilitation thesis support the conceptualization of BPD as a disorder in which emotional dysregulation plays a central role at the behavioral, cognitive, and neural levels. Our research demonstrated the importance of emotional impulsivity, particularly negative urgency, as a key factor associated with clinical severity and adverse outcomes. Further, neuroimaging findings highlighted neural alterations related to emotion processing, self-referential thinking, and traumatic experiences. Based on these findings, we implemented and investigated several targeted treatment approaches focused on enhancing emotion regulation, including Dialectical behavior therapy, fMRI neurofeedback, and repetitive transcranial magnetic stimulation. Together, these activities contributed not only to advancing scientific knowledge but also to the development and dissemination of evidence-based care for patients with BPD in the Czech Republic. Continued integration of research and clinical practice is essential for further improving the understanding and treatment of this complex disorder.

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List of peer-reviewed articles of the candidate

Articles published in a scholarly journal listed in the WoS database

2026

[1] SMAK, Pavel, Robin KOTOUCEK, Katarina KOSTOLANSKA, Eliska BARTECKOVA, Jan JURICA, Libor USTOHAL, Jana HORINKOVA, **Pavla LINHARTOVA**, Ondrej PES, Martin CUTA, Eva TABORSKA and Jana GREGOROVA. Liquid chromatography mass spectrometry of segmented hair cortisol - A Bayesian retrospective window. Journal Of Pharmaceutical And Biomedical Analysis [online]. 2026, 267(117127, Article 117127). ISSN 1873-264X. Available at: doi:10.1016/j.jpba.2025.117127

IF = 3,1; PHARMACOLOGY & PHARMACY Q2

2024

[2] RADIMECKA, Monika, Adela LATALOVA, Martin LAMOS, Martin JANI, Patrik BARTYS, Alena DAMBORSKA, Pavel THEINER and **Pavla LINHARTOVA**. Facial emotion processing in patients with borderline personality disorder as compared with healthy controls: an fMRI and ECG study. Borderline Personality Disorder And Emotion Dysregulation [online]. 2024, 11(1, Article 4). ISSN 2051-6673. Available at: doi:10.1186/s40479-024-00245-4

IF = 2,700; median IF PSYCHIATRY – 2,500; PSYCHIATRY Q2

2023

[3] JURICKOVA, Veronika, **Pavla LINHARTOVA**, Petr ADAMEK, Andrea NICHTOVA, Jakub FIGUEROA, Marek PAV, Marek PREISS and Jan VEVERA. Behavioral inhibition in neutral and emotional contexts in acutely violent patients with schizophrenia spectrum disorders. Current Psychology [online]. 2023, 42(28), 24088–24096. ISSN 1936-4733. Available at: doi:10.1007/s12144-022-03415-1

IF = 2,500; PSYCHOLOGY, MULTIDISCIPLINARY Q2

[4] LATALOVA, Adela, Monika RADIMECKA, Martin LAMOS, Martin JANI, Alena DAMBORSKA, Pavel THEINER, Eliska BARTECKOVA, Patrik BARTYS, Helena VLCKOVA, Katarina SKOLIAKOVA, Tomas KASPAREK and **Pavla LINHARTOVA**. Neural correlates of social exclusion and overinclusion in patients with borderline personality disorder: an

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IF = 4,000; IF PSYCHIATRY Q1

2022

[5] SVERAK, Tomas, **Pavla LINHARTOVA** *(contribution author)*, Martin GAJDOS, Matyas KUHN, Adela LATALOVA, Martin LAMOS, Libor USTOHAL and Tomas KASPAREK. Brain Connectivity and Symptom Changes After Transcranial Magnetic Stimulation in Patients With Borderline Personality Disorder. Frontiers In Psychiatry [online]. 2022, 12(770353, Article 770353). ISSN 1664-0640. Available at: doi:10.3389/fpsyt.2021.770353

IF = 4,700; PSYCHIATRY Q2

2021

[6] SVETLAK, Miroslav, **Pavla LINHARTOVA**, Terezia KNEJZLIKOVA, Jakub KNEJZLIK, Barbora KOSA, Veronika HORNICKOVA, Kristyna JAROLINOVA, Klaudia LUCANSKA, Alena SLEZACKOVA and Rastislav SUMEC. Being Mindful at University: A Pilot Evaluation of the Feasibility of an Online Mindfulness-Based Mental Health Support Program for Students. Frontiers In Psychology [online]. 2021, 11(581086, Article 581086). ISSN 1664-1078. Available at: doi:10.3389/fpsyg.2020.581086

IF = 4,232; PSYCHOLOGY, MULTIDISCIPLINARY Q1

[7] **LINHARTOVA, Pavla**, Jan SIRUCEK, Anastasia EJOVA, Richard BARTECEK, Pavel THEINER and Tomas KASPAREK. Dimensions of Impulsivity in Healthy People, Patients with Borderline Personality Disorder, and Patients with Attention-Deficit/Hyperactivity Disorder. Journal Of Attention Disorders [online]. 2021, 25(4), 584–595. ISSN 1557-1246. Available at: doi:10.1177/1087054718822121

IF = 3,196; PSYCHOLOGY, DEVELOPMENTAL Q2

[8] KNEJZLIKOVA, Terezia, Miroslav SVETLAK, Tatiana MALATINCOVA, Robert ROMAN, Jan CHLADEK, Jana NAJMANOVA, Pavel THEINER, **Pavla LINHARTOVA** and Tomas KASPAREK. Electrodermal Response to Mirror Exposure in Relation to Subjective Emotional Responses, Emotional Competences and Affectivity in Adolescent Girls With

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2020

[9] HLAVATA, Pavlina, **Pavla LINHARTOVA**, Rastislav SUMEC, Pavel FILIP, Miroslav SVETLAK, Marek BALAZ, Tomas KASPAREK and Martin BARES. Behavioral and Neuroanatomical Account of Impulsivity in Parkinson's Disease. Frontiers In Neurology [online]. 2020, 10(1338, Article 1338). ISSN 1664-2295. Available at: doi:10.3389/fneur.2019.01338

IF = 4,003; NEUROSCIENCES Q2

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IF = 7,723; PSYCHIATRY Q1

[11] GRAF, Sylvie, **Pavla LINHARTOVA** and Sabine SCZESNY. The effects of news report valence and linguistic labels on prejudice against social minorities. Media Psychology [online]. 2020, 23(2), 215–243. ISSN 1532-785X. Available at: doi:10.1080/15213269.2019.1584571

IF = 3,824; PSYCHOLOGY, APPLIED Q2

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[12] BARTECEK, Richard, Jana HORINKOVA, **Pavla LINHARTOVA** and Tomas KASPAREK. Emotional impulsivity is connected to suicide attempts and health care utilization in patients with borderline personality disorder. General Hospital Psychiatry [online]. 2019, 56, 54–55. ISSN 1873-7714. Available at: doi:10.1016/j.genhosppsych.2018.11.008

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[13] **LINHARTOVA, Pavla** *(corresponding author)*, Adela LATALOVA, Barbora KOSA, Tomas KASPAREK, Christian SCHMAHL and Christian PARET. fMRI neurofeedback in emotion regulation: A literature review. Neuroimage [online]. 2019, 193, 75–92. ISSN 1095-9572. Available at: doi:10.1016/j.neuroimage.2019.03.011

IF = 5,902; NEUROSCIENCES Q1

[14] SVERAK, Tomas, Pavla LINHARTOVA, Matyas KUHN, Adela LATALOVA, Barbora BEDNAROVA, Libor USTOHAL and Tomas KASPAREK. Transcranial magnetic stimulation in borderline personality disorder - case series. Ceska A Slovenska Neurologie A Neurochirurgie [online]. 2019, 82(1), 48–52. ISSN 1802-4041. Available at: doi:10.14735/amcsnn201948

IF = 0,377; NEUROSCIENCES Q4

2018

[15] HLAVATA, Pavlina, Tomas KASPAREK, **Pavla LINHARTOVA**, Hana OSLEJSKOVA and Martin BARES. Autism, impulsivity and inhibition a review of the literature. Basal Ganglia [online]. 2018, 14, 44–53. ISSN 2210-5344. Available at: doi:10.1016/j.baga.2018.10.002

[16] FILIP, Pavel, **Pavla LINHARTOVA**, Pavlina HLAVATA, Rastislav SUMEC, Marek BALAZ, Martin BARES and Tomas KASPAREK. Disruption of Multiple Distinctive Neural Networks Associated With Impulse Control Disorder in Parkinson's Disease. Frontiers In Human Neuroscience [online]. 2018, 12(462, Article 462). ISSN 1662-5161. Available at: doi:10.3389/fnhum.2018.00462

IF = 2,870; PSYCHOLOGY Q2

2017

[17] **LINHARTOVA, Pavla** *(corresponding author)* and Tomas KASPAREK. Current models, tests and methodological aspects of impulsivity measuring in psychology and psychiatry. Ceskoslovenska Psychologie. 2017, 61(1), 29–42. ISSN 1804-6436.

IF = 0,193; PSYCHOLOGY, MULTIDISCIPLINARY Q4

2014

[18] SIRUCEK, Jan, Adam TAPAL and **Pavla LINHARTOVA**. Need for cognition: Psychometric properties of the Czech version of the short Need for Cognition Scale. Ceskoslovenska Psychologie. 2014, 58(1), 52–61. ISSN 1804-6436.

IF = 0,239; PSYCHOLOGY, MULTIDISCIPLINARY Q4

2013

[19] **LINHARTOVA, Pavla**, Adam TAPAL, Lubos BRABENEC, Radomir MACECEK, Jan Jiri BUCHTA, Jakub PROCHAZKA, Stanislav JEZEK and Martin VACULIK. The Color Black And Situational Context: Factors Influencing Perception Of An Individual's Aggressiveness And Respectability. Studia Psychologica. 2013, 55(4), 321–333. ISSN 0039-3320.

IF = 0,414; PSYCHOLOGY, MULTIDISCIPLINARY Q4

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2022

[1] RADIMECKA, Monika, Petra JERABKOVA, Adéla LATALOVA and **Pavla LINHARTOVA**. Psychometric properties of the Czech version of Borderline Symptom List 23 (BSL-23); [PSYCHOMETRICKÉ VLASTNOSTI ČESKÉ VERZE BORDERLINE SYMPTOM LIST 23 (BSL-23)]. Psychoterapie. 2022, 16(1), 85–101. ISSN 1802-3983.

Category: Psychiatry and Mental Health – SJR Q4

2021

[2] THEINER, Pavel, **Pavla LINHARTOVA** and Adela LATALOVA. Dialectical behavioral therapy; [DIALEKTICKA BEHAVIORALNI TERAPIE]. Psychoterapie. 2021, 15(1), 23–29. ISSN 1802-3983.

Category: Psychiatry and Mental Health – SJR Q4

[3] LATALOVA, Adela, **Pavla LINHARTOVA** and Tomas KASPAREK. Dialectical behavior therapy for patients with borderline personality disorder: A literature review; [Dialektická behaviorální terapie u pacientů s hraniční poruchou osobnosti: Literární přehled]. Ceska a Slovenska Psychiatrie. 2021, 117(1), 26–32. ISSN 1212-0383.

Category: Psychiatry and Mental Health – SJR Q4

2017

[4] **LINHARTOVÁ, Pavla** *(corresponding author)*, Jan ŠIRŮČEK, Richard BARTEČEK, Pavel THEINER, Barbora JEŘÁBKOVÁ, Daniela RUDIŠINOVÁ and Tomáš KAŠPÁREK. Czech versions of impulsivity self-report scales the Barratt Scale and the UPPS-P Scale and their psychometric properties; [České verze sebeposuzovacích modelů impulzivity Barrattovy škály a škály UPPS-P a jejich psychometrické charakteristiky]. Ceska a Slovenska Psychiatrie. 2017, 113(4), 149–157. ISSN 1212-0383.

Category: Psychiatry and Mental Health – SJR Q4

Article published in another peer-reviewed journal (not listed in the above categories)

2021

[1] RADIMECKÁ, M., Adéla LÁTALOVÁ, Pavel THEINER a Pavla LINHARTOVÁ. Neurální mechanismy efektu dialektické behaviorální terapie u pacientů s hraniční poruchou osobnostií. Psychiatrie: časopis pro moderní psychiatrii [online]. 2021, 25(Suppl. 1), 23–23. ISSN 1211-7579. Dostupné z: https://www.medvik.cz/link/bmc21013199

[2] LÁTALOVÁ, Adéla, Pavla LINHARTOVÁ, Pavel THEINER a Tomáš KAŠPÁREK. Dialektická behaviorální terapie u pacientů s hraniční poruchou osobnosti: představení programu Psychiatrické kliniky Fakultní nemocnice Brno. Psychiatrie: časopis pro moderní psychiatrii [online]. 2021, 25(Suppl. 1), 21–21. ISSN 1211-7579. Dostupné z: https://www.medvik.cz/link/bmc21013194