Correlates of neurocognitive and social-cognitive functioning in major depressive disorder and borderline personality disorder

Doctoral (Ph.D.) thesis

Nándor Németh

Supervisors:
Prof. Tamás Tényi, M.D., D.Sc.
Mária Simon, M.D., Ph.D.

Leader of Doctoral Program:
Prof. Tamás Tényi, M.D., D.Sc.

Leader of Doctoral School:
Prof. Sámuel Komoly, M.D., D.Sc.

University of Pécs, Faculty of Medicine
Doctoral School of Clinical Neurosciences
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Abbreviations

ATT	Advanced Theory of Mind Test
BDI	Beck Depression Inventory
BMI	Body mass index
BPD	Borderline personality disorder
CAMS	Cartoon-Based Assessment of Mentalizing Skills
CPT	Conners' Continuous Performance Test-II
CTQ	Childhood Trauma Questionnaire-Short Form
CTQ EA	CTQ Emotional Abuse scale
CTQ EN	CTQ Emotional Neglect scale
CTQ PA	CTQ Physical Abuse scale
CTQ PN	CTQ Physical Neglect scale
CTQ SA	CTQ Sexual Abuse scale
CVD	Cardiovascular disease
EAT	Expression Attribution Test
ED	Eating disorder
EF	Executive functioning
ELS	Early life stress
FBPST	False-Belief Picture Sequencing Task
FPT	Faux Pas Test
FT	Flanker Task
GSI	Global severity index
HC	Healthy control
HDL-C	High-density lipoprotein cholesterol
IQ	Intelligence quotient
JAT	Joke-Appreciation Task
LDL-C	Low-density lipoprotein cholesterol
LFT	Letter Fluency Task
LST	Listening Span Task
MA	Meta-analysis
MASC	Movie for the Assessment of Social Cognition
MDD	Major depressive disorder
MDE	Major depressive episode
MET	Multifaceted Empathy Test

MSAT	Mental State Attribution Task
NTT	Nonverbal ToM Task
PTSD	Post-traumatic stress disorder
RMET	Reading the Mind in the Eyes Test
SCL-90-R	Symptom Check List-90-Revised
SUD	Substance use disorder
TAS-20	Toronto Alexithymia Scale-20 items
TASIT	The Awareness of Social Inference Test
TC	Total cholesterol
TG	Triglycerides
ToM	Theory of mind
WCST	Wisconsin Card Sorting Test

1. General introduction

The role of neurocognitive and social-cognitive abilities in psychiatric disorders received much attention in clinical research over the past decades. This thesis examines the correlates of neurocognitive and social-cognitive functioning in major depressive disorder (MDD) and borderline personality disorder (BPD). During my Ph.D. years, I was involved in two research projects. One line of research has focused on the biological and psychological effects of early stressful life events in patients with MDD. The first study of this thesis presents the results in this field. This study investigated the associations between depression, early life adversity, lipid parameters, and neurocognitive performance.

It is well known that early life stress (ELS; i.e., stress caused by traumatic experiences during childhood) is a strong predictor of MDD in adulthood (Lindert et al., 2014; Mandelli et al., 2015). However, not all adult MDD patients experienced ELS as a child. Clinical research suggests that MDD with a history of ELS is an etiologically distinct subtype of MDD with different symptomatology, course, and prognosis (Miniati et al., 2010; Klein et al., 2009; Nanni et al., 2012). One of the central issues of depression research today is the identification of features of MDD that may be related to the depressive psychopathology itself, and that may be rather due to the adverse effects of ELS (Heim et al., 2008). Initial research in this area suggests that many of the biological markers previously thought to be central to MDD are not a common feature of the disorder, but are primary characteristics of those MDD patients who experienced high levels of stress in childhood (Heim et al., 2000; Vythilingam et al., 2002). The first study of this paper aimed to extend this line of research.

Among others, serum lipids and lipoproteins have been suggested to be useful biomarkers for the diagnosis and therapy of MDD (for a review, see Parekh et al., 2017). However, studies investigating serum lipid composition in MDD yielded inconsistent findings (Shin et al., 2008; Persons and Fiedorowicz, 2016). Several hypotheses can be put forward to explain these contradictory results, such as methodological differences in the evaluation of depression, or the demographic, lifestyle, and clinical features of the patients involved in the studies. However, several other studies demonstrated associations between ELS and serum lipid alterations in different psychiatric (McIntyre et al., 2012; Misiak et al., 2015) and non-psychiatric samples (van Reedt Dortland et al., 2012; Spann et al., 2014). Thus, ELS might have been an uncontrolled confounding variable in studies on lipid disturbances in MDD that may have contributed to the inconsistent findings. The first study

presented in this thesis aims to explore whether lipid and lipoprotein abnormalities in MDD are primarily related to the disorder itself or can be attributed to the long-term detrimental effects of ELS. Research on this topic may extend our knowledge about the biological characteristics of an ELS-related subtype of MDD and may provide useful information for clinicians to identify depressed patients at high risk of somatic illnesses like metabolic syndrome or cardiovascular diseases.

Furthermore, the relationship between lipid profiles and neurocognitive functioning in patients with MDD has gained little attention so far. Neurocognitive impairments are frequently reported in MDD (for a review, see Rock et al., 2014), and they are frequently associated with impaired social and occupational functioning (Jaeger et al. 2006; Yen et al . 2011), more severe symptomatology (McDermott and Ebmeier, 2009), and poor response to antidepressant treatment (Potter et al. 2004; Story et al. 2008). Moreover, a recent meta-analysis (Motter et al., 2016) has found that cognitive training can improve symptom severity, daily functioning together with the cognitive processes in MDD. Because of these clinical implications, understanding factors that influence neurocognitive deficits in MDD is crucial. Some evidence suggests that neurocognitive impairments are much more pronounced in MDD patients with ELS (Dannehl et al., 2017). On the other hand, previous studies have found associations between serum lipid levels and neurocognitive performance in various non-elderly samples (Gendle et al., 2008; Sims et al., 2008; Lindenmayer et al., 2012). In line with this, a recent study documented elevated triglyceride levels in patients with MDD, which was associated with deficits in several neurocognitive domains (Shao et al., 2017). Based on these prior investigations, the first study of this thesis also aimed to investigate whether there were differences in attentional and executive abilities in MDD patients with and without a history of ELS and whether MDD patients' cognitive performance was related to the various serum lipid components.

Another line of the research (the second and third studies) presented in this thesis has focused on the mentalizing abilities of patients with borderline personality disorder. In recent years, the mentalization-based model of BPD (Bateman and Fonagy, 2010; Sharp and Kalpakci, 2015; Fonagy and Luyten, 2016) has received growing attention. Mentalization refers to social-cognitive processes that allow us to understand our own and others' behavior in terms of internal mental states (Bateman and Fonagy, 2016). Several abilities fall under the umbrella term of mentalization, such as empathy, emotional awareness, or theory of mind (ToM). According to the mentalization-based approach, the symptoms of BPD can be best explained as a consequence of impairments in these abilities (Sharp and Kalpakci, 2015;

Fonagy and Luyten, 2016). In earlier theoretical formulations (e.g., Fonagy et al., 2000), it was hypothesized that BPD patients have a generalized deficit in mentalizing. However, over time, several studies have shown that BPD patients' mentalizing abilities are not equally impaired: some subprocesses can be normal or even enhanced abilities can occur in specific domains of mentalization (for reviews, see Dinsdale and Crespi, 2013; Roepke et al., 2013). Based on these findings, recent theoretical formulations define mentalization as a multi-dimensional construct involving several dimensions along which various mentalizing subprocesses can be dissociated (Bateman and Fonagy, 2016). According to this novel approach, patients with BPD could be characterized by a specific mentalizing profile, i.e., they have deficits in controlled, cognitive, and internally-based forms of mentalization, but not in automatic, affective, and externally-based modes of mentalization (Fonagy and Luyten, 2016). Current research focuses on the exploration of BPD patients' mentalizing profile and the clinical and cognitive correlates of its components (Baez et al., 2015; Petersen et al., 2016; Berenson et al., 2018; Pluta et al., 2018). The identification of strengths and weaknesses in the mentalizing profile of BPD patients may provide important clues for further development of psychosocial interventions, which focus on the patients' mentalizing capacities (Bateman and Fonagy, 2010, 2016). Such an approach may help determine impaired mentalizing abilities that need to be improved by specific interventions, and abilities that are relatively preserved and can compensate deficits in other domains of mentalization. The second and third studies in this thesis present our contributions to this field.

In the second study, we performed a meta-analysis of the literature on theory of mind performances in patients with BPD. ToM is the other-oriented aspect of mentalization by which individuals can attribute mental states to other individuals (Choi-Kain and Gunderson, 2008). In recent years, several distinct subcomponents of ToM were identified (Bora et al., 2006; Shamay-Tsoory et al., 2006), thus, the study of ToM provides a good opportunity to characterize the mentalizing profile of BPD. For this purpose, we conducted separate meta-analyses for different ToM components, such as mental state decoding and mental state reasoning, as well as affective and cognitive ToM, and examined the potential dissociations of these abilities in BPD. Furthermore, we also investigated which demographic variables and psychiatric comorbidities may have an impact on borderline patients' ToM capacities.

The third study of the thesis was built upon the findings of our meta-analysis. In this study, we aimed to investigate the neurocognitive correlates of BPD patients' mentalizing profile. An intriguing research question in studying mentalizing abilities is the relationship

between these abilities and other non-social, domain-general cognitive skills, such as executive functioning (EF). EF refers to a set of neurocognitive capabilities that enable flexible responses in complex situations through the higher-order control of mental processes and behavior (Chan et al., 2008).

Several studies have demonstrated deficits of EF (reviewed by McClure et al., 2016) and mentalization in BPD (reviewed by Roepke et al., 2013); however, little research has explored the possible relationship between these two types of deficits (for one exception, see Baez et al., 2015). The majority of previous studies investigated EF concerning symptoms of affective and behavioral dysregulation in BPD (e.g., Fertuck et al., 2006; LeGris and Van Reekum, 2006). Nonetheless, one can assume that executive impairments may contribute to the interpersonal problems in BPD like in other psychiatric conditions. Supposing that EF deficits play an important role in mentalizing difficulties in BPD, the integration of cognitive remediation programs into the routine psychosocial interventions in BPD may help to achieve stronger therapeutic effects on patients' interpersonal functioning. Based on these considerations, we investigated the relationship between EF and mentalizing in BPD in the third study of this thesis. The first aim of this study was to analyze simultaneously the mentalizing and executive abilities in BPD patients on tasks assessing different subdomains of mentalization and EF. Here, we examined both other- and self-oriented mentalization, which we operationalized as ToM and emotional self-awareness/alexithymia, respectively. As the results of our meta-analysis suggested that BPD patients have intact mental state decoding capacity but deficits in mental state reasoning, we investigated these two aspects of ToM separately. An additional goal of this study was to determine the relative importance of BPD diagnosis and EF in predicting mentalizing performance while considering the potential effects of co-occurring psychiatric symptoms and general intelligence.

2. Examining the relationships between early life stress, serum lipid profiles, and cognitive functioning in major depressed patients

2.1. Introduction

Major depressive disorder (MDD) is a key public health concern today (Kessler, 2012), as it is a commonly occurring and often-recurring condition associated with considerable functional impairments, diminished quality of life, increased medical morbidity, and mortality (Kessler and Bromet, 2013). In addition to mental health problems, MDD often coincides with somatic illnesses such as metabolic syndrome (Pan et al., 2012) and cardiovascular diseases (CVD) (Hare et al., 2014); nevertheless, the direction of the causal relationship between depression and cardiometabolic diseases, as well as the specific underlying mechanisms, have not yet been fully understood. Moreover, patients suffering from MDD often present neurocognitive deficits (Austin et al., 2001; McDermott and Ebmeier, 2009; Lee et al., 2012; McIntyre et al., 2013; Rock et al., 2014).

Major depressive disorder is a clinically heterogeneous disorder, which is a result of manifold etiological factors, as well as developmental pathways. Early life stress (ELS), such as adverse childhood experiences (e.g., physical, emotional, and sexual abuse, neglect, parental loss, and poverty), have long been known to be strong predictors of MDD in adulthood (e.g., Widom et al., 2007; Norman et al., 2012; Lindert et al., 2014). A recent meta-analysis of 26 studies revealed that childhood emotional abuse and neglect showed the strongest association with depression risk in adults, while sexual/physical abuse or family violence have been proved to be non-specific risk factors for various mental disorders (Mandelli et al., 2015).

MDD patients with a history of ELS are suggested to suffer from a clinically and biologically distinguishable, special subtype of depression according to the results of a series of studies (Heim et al., 2008). Adult MDD with prior ELS is associated with earlier onset, more severe symptomatology, a greater number and longer duration of depressive episodes, a tendency to be chronic or therapy-resistant, higher rates of psychiatric comorbidities, as well as suicidal behavior or impulsivity compared to MDD without ELS (Brodsky et al., 2001; Zlotnick et al., 2001; Klein et al., 2009; Wiersma et al., 2009; Hovens et al., 2010; Miniati et al., 2010; Nanni et al., 2012). The results of biological research suggest that many biomarkers previously associated with MDD, in general, are rather characteristic of only those MDD patients who experienced high amounts of stress in their childhood. For

example, significant differences were found between MDD patients with or without ELS in the stress reactivity of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system (Heim et al., 2000), as well as in the morphology of brain regions rich in glucocorticoid receptors (like the hippocampus) (Vythilingam et al., 2002)

Besides depression, ELS is also a risk factor for severe metabolic alterations and central obesity (Pervanidou and Chrousos, 2012; Davis et al., 2014) and CVD (Rich-Edwards et al., 2012; Loria et al., 2014). Furthermore, a recent study which analyzed data on cardiometabolic markers of 9000 cohort members found that physical and sexual abuse was associated with high low-density lipoprotein cholesterol (LDL-C) and low serum levels of high-density lipoprotein cholesterol (HDL-C), and that childhood neglect, as well as emotional abuse, was associated with raised triglycerides (TG) and lower HDL-C (Li et al., 2019). ELS appears to be related to adult cardiometabolic complications and comorbidities by two etiologic mechanisms: (1) the direct effect of early and late-life stress; (2) general factors that are compensatory behaviors, as well as attempts at self-help by food and agents (Kesebir, 2014).

Serum lipid concentrations have been widely investigated in MDD; however, studies yielded inconsistent results. Both higher (Ledochowski et al., 2003; Nakao and Yano, 2004; Moreira et al., 2017) and lower serum total cholesterol (TC) levels (Olusi and Fido, 1996; Maes et al., 1997; Ong et al., 2016) were registered in patients with MDD compared to healthy controls (HC), and null findings have also been reported (Lehto et al., 2008; van Reedt Dortland et al., 2010; Enko et al., 2018). Alterations of serum concentrations of LDL-C were most widely studied in MDD. Recently, a comprehensive meta-analysis found significantly lower cross-sectional LDL-C serum concentrations in MDD compared to HCs, when LDL-C was modeled as a continuous measure (Persons and Fiedorowicz, 2016). The authors suggested a U-shaped relationship between depression severity and LDL-C. Nevertheless, this meta-analysis did not consider the effect of ELS on LDL-C concentration in depression. Studies that investigated the relationship between HDL-C and MDD had produced contradictory findings. Some studies found no association at all (Aijänseppä et al., 2002; Rice et al., 2010), while others revealed a correlation between lower HDL-C and depression (Kim et al., 2004; Ancelin et al., 2010) and one study reported higher HDL-C than matched controls (Olusi and Fido, 1996). Similarly, contradictory findings have been published in serum triglyceride levels in depressed patients. Kinder and co-workers reported on a positive correlation between triglyceride blood levels and depression in women aged between 17 and 39 years (Kinder et al., 2004), and a positive correlation between triglyceride

blood levels and the Beck Depression Inventory (BDI) score was also found in women who had received coronary angiography (Vaccarino et al., 2008). But there are also negative findings demonstrating no difference in serum TG levels between control and depressed subjects (Pjrek et al., 2007).

A number of theories have been put forward to explain the contradictory findings on serum lipid disturbances in depression. Most of them emphasize the influence of the methodology used for the clinical evaluation of depression (e.g., dimensional or categorical assessment), or the impact of demographic, lifestyle, and clinical variables (van Reedt Dortland et al., 2010). However, some results imply that the inconsistent findings may be due to the heterogeneity of depression and that the lipid disturbances may be characteristic of certain depression subgroups only. Accordingly, for example, in some investigations, lipid alterations were detected particularly in depressive subjects with atypical or melancholic symptoms (Huang and Chen, 2004; van Reedt Dortland et al., 2010; Lamers et al., 2013), or suicidal tendencies (Wu et al., 2016).

Most previous works focusing on the association between depression and lipid profiles did not control for the effects of ELS. Since the prevalence of childhood adverse experiences is much higher in depressed patients than in the healthy population, ELS might be a confounding variable that may have affected the results of such studies, leading to contradictory findings. Considering that (1) the history of ELS is only present in a subgroup of depressed patients, and strong associations were found between ELS and serum lipid alterations both in psychiatric (McIntyre et al., 2012; Misiak et al., 2015) and non-psychiatric samples (van Reedt Dortland et al., 2012; Spann et al., 2014), moreover (2) lipid disturbances were detected mostly in depression with atypical or melancholic symptoms, or suicidal tendencies, which are more characteristic to depression with ELS (Harkness and Monroe, 2002; Matza et al., 2003; Klein et al., 2009), it is possible that lipid disturbances may accompany depression primarily with adverse early life stress.

So far, only a few studies considered the role of ELS in the association between depression and metabolic disturbances. McIntyre et al. (2012) found a significantly lower level of HDL-C in MDD patients who experienced childhood adversity, but there was no statistically significant difference in the overall rate of dyslipidemia and metabolic syndrome between subjects with and without childhood adversity. Ding et al. (2014) did a metabonomic analysis and reported that MDD patients had lower TC levels compared to controls, but patients with a history of sexual or physical abuse had higher TC levels compared to the MDD only group. Wingenfeld et al. (2017) conducted a women-only study

in a physically healthy clinical sample and found no difference in TG, cholesterol, HDL-C, LDL-C, and other metabolic risk markers between MDD patients with and without sexual or physical abuse. More recently Kraav et al. (2019) found decreased serum TC in MDD outpatients with a childhood history of physical violence.

Although these studies provided evidence that serum lipid alterations are related to ELS in MDD, they did not address the question of whether both depressive pathology and ELS have an independent influence on these alterations or lipid disturbances can be explained mainly by the effects of ELS. Only Wingenfeld et al. (2017) examined this issue explicitly; however, one should carefully interpret their findings, as the exclusion of obese individuals (with body mass index > 30 kg/m^2) might have led to an underrepresentation of subjects with existing obesity linked to ELS. Moreover, most previous research considered only the effects of certain types of ELS (mainly physical and sexual abuse) on lipid concentrations in MDD and did not investigate the effects of other types of ELS, such as emotional abuse and neglect, which are more relevant in the etiology of this disorder. In addition, the majority of earlier studies did not assess the overall serum lipid profile of participants and did not account for the potentially confounding influences of important lifestyle variables, like body mass index (BMI) or physical activity. Finally, although several studies demonstrated associations between different serum lipid levels and cognitive functioning in various psychiatric (Lindenmayer et al., 2012; Shao et al., 2017) and non-psychiatric samples (Gendle et al., 2008; Sims et al., 2008), none of the previous studies examined the possible relationships between ELS-related lipid alterations and cognitive performance of MDD patients.

2.2. Objectives

The primary aim of our study was to explore whether lipid and lipoprotein abnormalities in MDD are due to the depressive pathology itself, or rather, can be attributed to the adverse effects of ELS. To investigate this question, in the first step, we operationalized depression as a categorical variable based on the presence or absence of MDD diagnosis in our sample and performed group comparisons between patients with MDD and HC subjects. We first examined whether there are differences in the lipid profile between the HC group and the entire MDD group, and then we looked at how these differences change when MDD patients are divided into two subgroups, one with a history of ELS (MDD+ELS) and the other without (MDD Only). In the next step, we operationalized

depression as a continuous variable based on the severity of current depressive symptoms and investigated whether the severity of symptoms or the amount of ELS would be the better predictor of serum lipid and lipoprotein concentrations in the entire patient group.

The secondary aim of our study was to investigate whether serum lipid and lipoprotein abnormalities are associated with cognitive functioning in MDD. We predicted that patients with MDD+ELS would show poorer attentional and executive abilities compared to the HC and the MDD Only subjects and that their reduced cognitive performance would be related to their unfavorable lipid profile.

2.3. Methods

2.3.1. Participants

Forty-two patients with MDD and 20 healthy controls participated in this study. Patients with MDD were recruited from the Affective Disorder Unite of the Department of Psychiatry and Psychotherapy, University of Pécs. The local Research Ethics Committee of the University of Pécs approved the study design and protocol (Ethical Approval No.: 2015/5626) and all participants provided written informed consent. To exclude the effects of aging, only subjects aged between 18 and 55 were involved in the study, because several studies reported an increased prevalence of dyslipidemia in the elderly population (Bechtold et al., 2006; Shanmugasundaram et al., 2010; Liu and Li, 2015).

All patients fulfilled the DSM-5 diagnostic criteria of MDD (APA, 2013). Inclusion criteria of the MDD group included: (1) age 18–55 years; (2) a diagnosis of MDD in a current major depressive episode as assessed by a trained psychiatrist using the Structured Clinical Interview for DSM-5, Clinical Version, (SCID-5-CV; First et al., 2016) and the Structured Clinical Interview for DSM-5, Personality Disorders (SCID-5-PD; First et al., 2018). Exclusion criteria for the patient group were: current substance abuse or dependence (if the patient met diagnostic criteria, he or she had to be abstinent for at least 2 years), bipolar disorder, post-traumatic stress disorder, a history of any psychotic disorder, and current eating disorders. Healthy control participants were recruited by online advertisements and via personal contacts of the researchers. The control sample was screened by a qualified psychiatrist to ascertain the absence of a lifetime or family history of mental disorders. In addition, the Symptom Checklist-90-Revised questionnaire (Derogatis, 1977) was applied to rule out relevant subthreshold psychiatric symptoms in potentially healthy individuals.

Exclusion criteria for both the patients and the controls were: liver or kidney disease, severe cardiovascular disease, uncontrolled thyroid disorders, uncontrolled diabetes mellitus, and current inflammatory illness. Subjects with known familial hyperlipidemia were not included. Subjects with neurological disorders, in addition, those with a history of head injury and with severe hearing or visual impairment, and an IQ < 85 were also excluded.

In the MDD group, treatment with antidepressant medication or psychotherapy were not exclusion criteria once the diagnosis had been established. Current psychotropic medication data were collected: 41 (97.6%) MDD subjects were taking antidepressants (20 patients were taking SSRIs, 12 mirtazapine, 2 mianserine, 2 venlafaxine, 1 duloxetine, 1 trazodone, 1 vortioxetine, 1 agomelatine), 21 (50%) low dose antipsychotics (17 quetiapine, 1 ziprasidone, 1 aripiprazole, 1 thiothixene), 5 (11.9%) mood-stabilizing medications. None of the control subjects took psychotropic medication.

One MDD patient was on lipid-lowering drug (atorvastatin) treatment at the time of the study. Two patients and two control subjects kept a vegetarian diet. The demographic, lifestyle, and clinical data are presented in Table 1.

2.3.2. Instruments

2.3.2.1. Laboratory analyses

Cubital venous blood was drawn from the participants between 7 and 8 AM in order to avoid any possible effect of circadian variations. The samples were collected following 8-12 hours of fasting. Serum concentrations of total cholesterol, LDL-C, HDL-C, and triglycerides were all measured with a Roche Modular (module P800) clinical chemistry analyzer, using enzymatic colorimetric test methods according to the manufacturer's instructions (Roche Diagnostics, Hungary).

2.3.2.2. Questionnaires

The severity of actual depressive symptoms was assessed using the Beck Depression Inventory (Beck et al., 1961; Hungarian adaptation: Pető et al., 1987; Rózsa et al., 1998). This is a 21-item self-report questionnaire rating the presence and extent of sadness, pessimism, past failure, loss of pleasure, self-dislike, self-criticism, and suicidal thoughts and wishes in the past week. The scores range from 0 to 63 points and higher scores indicate more severe depression. In this study, Cronbach's alfa values were excellent for the total

BDI scores (0.95) and the cognitive subscale scores (0.91) and good for the somatic-affective subscale (0.86).

ELS was surveyed with the 28-item retrospective self-report questionnaire of the Childhood Trauma Questionnaire-Short Form (CTQ; Bernstein et al., 2003), that assesses the severity of five types of maltreatment before the age of 18 years: physical abuse (CTQ PA), emotional abuse (CTQ EA), physical neglect (CTQ PN), emotional neglect (CTQ EN), and sexual abuse (CTQ SA). Each subscale is measured with five 5-point scale items. The short form of the questionnaire is the most widely used version, which includes clinical cut-offs for significant abuse and neglect. Childhood maltreatment exposure was entered in the statistical analyses as a continuous variable with row scores, or it was coded into a two-level variable for dividing the MDD sample into low-ELS and high-ELS subgroups. Patients with MDD were assigned to the MDD Only subgroup if they had not experienced any type of moderate to severe childhood trauma. MDD patients were put into the MDD+ELS subgroup if they had at least one type of moderate to severe childhood trauma. In the present sample, the internal consistencies were excellent for the CTQ total score, and for the subscales of physical abuse, emotional abuse, sexual abuse, as well as for emotional neglect (Cronbach's alphas > 0.9). The internal consistency was acceptable for the subscale of physical neglect (Cronbach's alpha = 0.77). The Hungarian translation of the original (English) CTQ was done using the back-translation procedure (Sperber, 2004). Two senior authors translated the English version to Hungarian. To ensure that the translated version is equivalent to the source version, a bilingual linguist translated the early Hungarian version back to English. Errors of meaning and conceptual inconsistencies between the translated versions were discussed and corrected.

2.3.2.3. Sociodemographic data

A self-report questionnaire determined the various sociodemographic data, including education, lifestyle habits of regular exercise. Measurements for height and body mass were obtained using a wall-mounted stadiometer and electronic scale, respectively. BMI was calculated as body mass in kilograms divided by height in meters squared.

2.3.2.4. Neurocognitive tests

Executive functions were assessed by the computerized version of the Wisconsin Card Sorting Test (WCST; Heaton, 1981). In the test, cards with geometric shapes (different in

their number, color, and form) have to be matched according to varying sorting principles. The actual method of sorting has to be found out by the subject based on the provided feedback (correct or incorrect). Besides the number of total correct responses and non-perseverative errors, we detected the number of perseverative errors and conceptual level responses as a measure of shifting ability and conceptual ability, respectively. The WCST is a commonly used cognitive measure in clinical investigations including the studies examining cognitive changes related to depression (see e.g., Li et al., 2010; Giel et al., 2012; McGirr et al., 2012). Moreover, the WCST has been found to be a highly reliable test already decades ago (e.g., Tate et al., 1998).

Attentional processes were assessed by the Conners' Continuous Performance Test-II (CPT; Conners, 2000). In this task, respondents are required to press the space bar when any letter except X appears. The inter-stimulus intervals are variable (1, 2 or 4 s) with display time of 250 ms. There are six blocks, with three sub-blocks each containing 20 trials. The procedure takes 14 min to complete. Omission errors and commission errors, as well as hit reaction time and detectability (a measure of the difference between the signal [non-X] and noise [X] distributions), were assessed.

CPT is one of the most widely used, computer-administered cognitive tests of attention and impulsivity. Since it is not a verbal test, and no language adaptation is necessary thus, the reliability testing of this test was out of the scope of our study. A recent publication reported that CPT has a strong internal consistency, adequate test-retest reliability for commission errors and response time, and a relatively poor test-retest reliability for omission errors, and practice effects for omission and commission errors (Shaked et al., 2019). Moreover, CPT performances were unrelated to those in other cognitive tests, such as the Stroop Color-Word test (Shaked et al., 2019). CPT is often used in clinical research on depression (see e.g., Godard et al., 2011; Parlar et al., 2016).

2.3.3. The sequence of data collection

Research participants underwent the following study procedures. First, the clinical interviews and questionnaires were completed to assess the severity of depression and early life stress. Then, a senior clinician blinded to the results of the CTQ data conducted a semi-structured interview about the stressful life events during childhood and adolescence. CTQ scores and the interview responses were compared, discrepancies were discussed with the participants. In the case of unresolvable discrepancies, participants were excluded from the

study (*n*=3). Cognitive functions were assessed separately the next day or the day after the next day. Blood samples were taken in the morning within 24 hours after the initial clinical assessments.

2.3.4. Statistical analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS), version 21.0. Normality was checked by normal probability plots and by the Shapiro-Wilk and the Kolmogorov-Smirnov tests. Lipid and cognitive variables that showed skewed distributions were log-transformed, and all subsequent analyses were done with these transformed data. Between-group differences in demographic, lifestyle, and clinical variables were analyzed by the chi-square test and by ANOVA or non-parametric tests (Mann-Whitney U and Kruskal-Wallis). Differences between the study groups in the serum lipid and lipoprotein values, as well as cognitive performances, were tested first by one-way ANOVA. If the homogeneity assumption (tested by Levene's statistic) was violated, Welch-probe was used for the group comparisons. Fisher's LSD and Games-Howell tests were applied for post-hoc pairwise comparisons. In the next step, between-group differences in the main variables were analyzed using ANCOVA with demographic and lifestyle variables as covariates and post-hoc comparisons were done with Bonferroni correction.

After the group comparisons, hierarchical multiple linear regression analyses were run in the entire MDD group to explore whether the heterogeneity of lipid and lipoprotein levels were explained rather by the severity of depression or by the severity of ELS and whether there were associations between the revealed lipid alterations and the patients' cognitive performances. Due to the relatively large number of background variables and the relatively small sample size, in the regression analyses, we selected the most relevant confounders using the Forward procedure, and predictor variables of main interest were added to the models with the Enter method. In the Forward procedure, the predictor variables were sequentially included in the regression models depending on the strength of their correlation with the criterion variable (*P* to enter < 0.05). The Enter procedure enters the predictor variables in the models irrespective of their significance with the criterion. In all analyses, *P*-values (two-tailed) below 0.05 were considered statistically significant. Effect sizes were measured by calculating Cohen's *d* (for between-group comparisons) as well as Cohen's f^2 (for multiple regression analyses).

2.4. Results

2.4.1. Demographic, lifestyle, and clinical data

2.4.1.1. Two-group comparisons: healthy controls versus the entire MDD group

There were no significant between-group differences in age ($F_{(1,60)}$=0.024, P=0.877), gender ratio ($X^2_{(1)}$=1.303, P=0.254), BMI (U=398.000, Z=-0.331, P=0.740), and regular physical activity (U=345.500, Z=-1.167, P=0.243). The level of education was significantly lower (U=190.000, Z=-3.612, P<0.001), while the BDI score, as well as all CTQ scores (including total score and trauma type subscores) were significantly higher in MDD patients compared to the healthy subjects (BDI: Welch's $F_{(1,47.7)}$=146.324, P<0.001); CTQ Total: U=72.500, Z=-5.238, P<0.001; CTQ PN: U=110.000, Z=-4.787, P<0.001; CTQ PA: U=186,500, Z=-3.790, P<0.001; CTQ EN: $F_{(1,60)}$=26.407, P<0.001; CTQ EA: U=116.500, Z=-4,585, P<0.001; CTQ SA: U=230.000, Z=-3.506, P<0.001) (for details, see Table 1).

2.4.1.2. Three-group comparisons: healthy controls versus MDD Only versus MDD+ELS

The three groups did not differ in age ($F_{(2,59)}$=0.125, P=0.883), gender ratio ($X^2_{(2)}$=1.428, P=0.490), BMI ($X^2_{(2)}$=0.142, P=0.931), and physical activity ($X^2_{(2)}$=3.083, P=0.214), however, a significant difference could be observed between groups in years of education ($X^2_{(2)}$=14.079, P=0.001). Pairwise comparisons showed that the level of education was significantly lower in the MDD Only and in the MDD+ELS groups compared to HC (P=0.025, P=0.001, respectively). As expected, CTQ total score, and the specific trauma subscores were significantly different between groups (CTQ Total: $X^2_{(2)}$=46.768, P<0.001; CTQ PN: $X^2_{(2)}$=34.441, P<0.001; CTQ PA: $X^2_{(2)}$=30.924, P<0.001; CTQ EN: $F_{(2,59)}$=43.020, P<0.001; CTQ EA: $X^2_{(2)}$=37.808, P<0.001; CTQ SA: $X^2_{(2)}$=23.897, P<0.001) and post-hoc comparisons revealed that the MDD+ELS group had significantly higher scores in all CTQ scales than the MDD Only group (CTQ Total: P<001; CTQ PN: P=0.002; CTQ PA: P<0.001; CTQ EN: P<0.001; CTQ EA: P<0.001; CTQ SA: P=0.002) (Table 1). The severity of ELS was significantly higher for physical and emotional neglect in the MDD Only group compared to HC (CTQ PN: P=0.039; CTQ EN: P=0.012), but there was no significant difference in CTQ total score, as well as in physical, emotional, and sexual abuse between these two groups (CTQ Total: P=0.051; CTQ PA: P=0.596; CTQ EA: P=0.149;

CTQ SA: P=0.515). There was a significant difference between study groups in BDI score (Welch's $F_{(2.29,0)}$=80.404, P<0.001) and the pairwise comparisons demonstrated that both MDD subgroups had significantly higher BDI score than the HC group (P<0.001), whereas depression severity was similar in the two MDD subgroups (P=0.113) (Table 1).

TABLE 1. Demographic, lifestyle, and clinical characteristics of patients with MDD and HCs.

	HC (*n*=20)	Entire MDD (*n*=42)	MDD Only (*n*=21)	MDD+ELS (*n*=21)
Demographic and lifestyle characteristics				
Age (years)[a]	35.80 (8.53)	35.40 (9.73)	34.71 (8.17)	36.10 (11.24)
Gender (female/male)	13/7	33/9	17/4	16/5
Education (years)[b]	15.00 (5.00)	12.00 (1.00) ***	12.00 (2.00) §	12.00 (1.00) §§
Physical exercise per week (hours)	1-2	2-4	1-2	2-4
Body mass index (kg/m^2)[b]	23.39 (6.6)	23.11 (5.26)	23.12 (5.69)	23.11 (4.83)
Early life stress				
CTQ physical neglect[b]	5.00 (1.00)	9.00 (4.00) ***	7.00 (4.50) §	10.00 (5.50) $^{\S\S\S\ ++}$
CTQ physical abuse[b]	5.00 (0.00)	7.00 (5.25) ***	5.00 (2.00)	10.00 (5.50) $^{\S\S\S\ +++}$
CTQ emotional neglect[a]	9.10 (3.51)	13.40 (5.42) ***	11.95 (3.56) §	18.95 (3.47) $^{\S\S\S\ +++}$
CTQ emotional abuse[b]	6.00 (2.75)	13.50 (10.25) ***	9.00 (5.50)	19.00 (5.00) $^{\S\S\S\ +++}$
CTQ sexual abuse[b]	5.00 (0.00)	5.00 (4.25) ***	5.00 (0.50)	9.00 (7.50) $^{\S\S\S\ ++}$
CTQ total score[b]	29.00 (11.5)	54.50 (29.50) ***	40.00 (17.00)	69.00 (18.50) $^{\S\S\S\ +++}$
Clinical data				
BDI total score[a]	3.00 (2.13)	23.21 (10.38) ***	20.05 (10.29) §§§	26.38 (9.69) §§§
Age at the onset of MDD[b]	-	25.5 (17-32.25)	28 (18-34)	20 (16-31.5)
Number of lifetime depressive episodes [b]	-	2 (1.75-3)	2 (1-3)	2 (2-3)
Double depression (*n*)	-	2	1	1
Chronic depression (*n*)	-	5	1	4
Recurrent depression (*n*)	-	31	13	18
Lipid profile				
Total cholesterol (mmol/L)[a]	4.85 (0.91)	5.10 (1.08)	5.04 (0.88)	5.16 (1.27)
Triglycerides (mmol/L)[b]	0.89 (0.93)	1.06 (0.78)	0.92 (0.39)	1.26 (1.05) $^{+}$
HDL cholesterol (mmol/L)[a]	1.65 (0.33)	1.58 (0.37)	1.70 (0.40)	1.45 (0.28) $^{+}$
LDL cholesterol (mmol/L)[a]	2.73 (0.77)	2.95 (0.79)	2.87 (0.61)	3.03 (0.95)
LDL-C/HDL-C[b]	1.75 (0.78)	1.81 (1.05)	1.70 (0.69)	2.00 (1.33)
TC/HDL-C[b]	3.04 (1.13)	3.22 (1.29)	3.04 (1.03)	3.27 (1.78) $^{\S\ +}$

[a] Means and standard deviations are presented. [b] Medians and inter-quartile ranges are presented. Two-group comparisons: overall MDD group compared to HC: * P<0.05, ** P<0.01, *** P<0.001. Three-group comparisons: MDD Only compared to MDD+ELS: $^{+}$ P<0.05, $^{++}$ P<0.01, $^{+++}$ P<0.001. MDD Only or MDD+ELS compared to HC: § P<0.05, §§ P<0.01, §§§ P<0.001. BDI, Beck Depression Inventory; CTQ, Childhood Trauma Questionnaire-Short Form; ELS, early life stress; HC, healthy controls; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDD, major depressive disorder; TC, total cholesterol.

2.4.2. Lipid profile

2.4.2.1. Two-group comparisons: healthy controls versus the entire MDD group

No difference was found between the two groups by one-way ANOVA when we compared serum TC ($F_{(1,60)}$=0.782, P=0.380), TG ($F_{(1,60)}$=0.426, P=0.516), HDL-C ($F_{(1,60)}$=0.609, P=0.438), LDL-C ($F_{(1,60)}$=1.062, P=0.307), and the two atherogenic indices (LDL-C/HDL-C: $F_{(1,60)}$=2.052, P=0.157, TC/HDL-C: $F_{(1,60)}$=2.036, P=0.159) (Table 1). To control for the effects of demographic and lifestyle variables on lipid and lipoprotein levels, ANCOVAs were conducted with age, gender, level of education, physical exercise, and BMI as covariates, but again no significances were found (Figure 1; Supplementary Table 1).

2.4.2.2. Three-group comparisons: healthy controls versus MDD Only versus MDD+ELS

Results of the ANOVA omnibus tests indicated significant between-group differences in TG (Welch's $F_{(2,35.4)}$=4.367, P=0.020), HDL-C ($F_{(2,59)}$=3.293, P=0.044), and TC/HDL-C ($F_{(2,59)}$=3.434, P=0.039). Post-hoc comparisons (Fisher's LSD and Games-Howell tests) showed that the level of HDL-C was significantly lower (P=0.018), while the level of TG (P=0.015) and also the ratio TC/HDL-C (P=0.034) were significantly higher in the MDD+ELS than in the MDD Only group. The ratio of TC/HDL-C of the MDD+ELS group was also significantly higher when compared to the HC group (P=0.022) There were no significant differences between groups in TC (Welch's $F_{(2,38.7)}$=4.367, P=0.645), LDL-C ($F_{(2,59)}$=0.733, P=0.485), and LDL-C/HDL-C ($F_{(2,59)}$=2.562, P=0.086) (Table 1). Cohen's d values for all significant group differences ranged from 0.68 to 0.78 indicating medium-to-large effect sizes.

After controlling for the effects of age, gender, level of education, physical exercise, and BMI by ANCOVA, between-group differences remained significant in TG ($F_{(2,54)}$=6.320, P=0.003), HDL-C ($F_{(2,54)}$=3.409, P=0.040), and TC/HDL-C ($F_{(2,54)}$=4.854, P=0.012), and a new significant difference emerged in LDL-C/HDL-C ($F_{(2,54)}$=3.794, P=0.029). As it is shown in Figure 1, post-hoc Bonferroni comparisons demonstrated that HDL-C was significantly lower in MDD patients with ELS than in MDD Only patients, as well as the TG and the TC/HDL-C index, were significantly higher in the MDD+ELS group compared both to the MDD Only and to the HC groups. Moreover, a higher LDL-C/HDL-C

ratio was revealed in MDD+ELS patients relative to the HC. There were no significant differences between groups by ANCOVA in TC ($F_{(2,54)}$=0.742, P=0.481) and LDL-C ($F_{(2,54)}$=1.454, P=0.243) (Figure 1). For the significant group comparisons, Cohen's d values ranged from 0.63 to 0.94 (medium-to-large effect sizes).

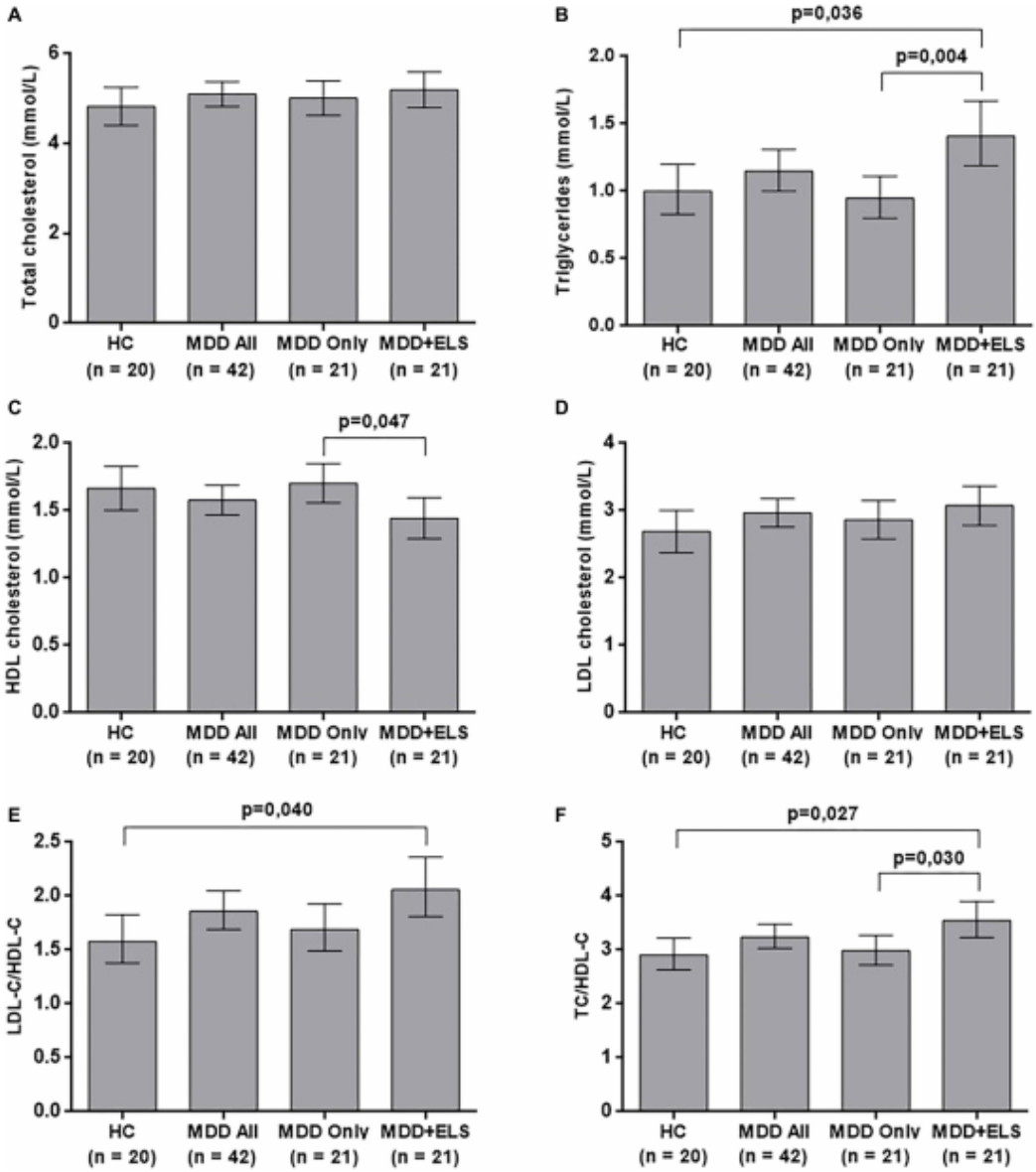

FIGURE 1. Serum lipid and lipoprotein levels in HCs and MDD patients after the adjustment for age, gender, education, physical exercise per week, and body mass index. (**A**) total cholesterol levels; (**B**) triglyceride levels; (**C**) high-density lipoprotein cholesterol levels; (**D**) low-density lipoprotein cholesterol levels; (**E**) LDL-C/HDL-C ratio; (**F**) TC/HDL-C ratio. The bars represent the means and upper and lower 95% confidence intervals of the examined lipid profile elements. The values of triglycerides, LDL-C/HDL-C, and TC/HDL-C are results of back-transformation (antilog) because of the skewed distribution of the original data. The *P*-values of significant differences are shown. ELS, early life stress; HC, healthy controls; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDD, major depressive disorder; TC, total cholesterol.

2.4.2.3. Multiple linear regression analyses: the effects of depression severity and ELS on serum lipid/lipoprotein levels

Next, we performed a series of hierarchical linear regression analyses in the entire MDD group to determine whether the heterogeneity of each lipid/lipoprotein level is explained by the severity of depression or by the amount of ELS after controlling for each other and potentially confounding factors. Relevant confounders were selected from the demographic variables (age, gender, years of education) in Block 1, and from the lifestyle variables (BMI, physical exercise per week) in Block 2 using the Forward variable selection procedure. Because we were interested in how the statistical effect of current depression severity on lipid/lipoprotein levels changes after including ELS in the models, next, in Block 3, depression severity (BDI score), and finally, in Block 4, the amount of early life stress (CTQ total score) were added to the regression models using the Enter method.

After running hierarchical regression analyses for each lipid and lipoprotein parameters as dependent variables, we found that in Block 3, the BDI score predicted only HDL-C (P=0.010) significantly. However, when the CTQ total score was also added in Block 4, the relationship between BDI and HDL-C lost its significance (P=0.068) and no other significantly predictive relationship emerged between depression severity and any of the lipid profile elements (Table 2). However, in Block 4, the severity of ELS had a significant negative association with HDL-C level (P=0.040) and a significant positive association with the serum level of TG (P=0.014) and TC/HDL-C index (P=0.043). Cohen's f^2 values for these significant associations ranged from 0.11 to 0.18 indicating moderate effect sizes.

TABLE 2. Hierarchical linear regression analyses predicting serum lipid and lipoprotein levels in the entire MDD group.

Dependent variable	Blocks	Predictors	R^2	ΔR^2	β	β'
Total cholesterol	Block 1 (forward)	Age	0.157	0.157	0.396**	0.381**
	Block 2 (forward)	Body mass index	0.304	0.147	0.384**	0.382**
	Block 3 (enter)	**Depression severity**	0.311	0.007	-0.084	-0.080
	Block 4 (enter)	**Early life stress**	0.312	0.000		-0.013
Tryglicerides	Block 1 (forward)	No variable associated				
	Block 2 (forward)	Physical exercise	0.108	0.108	-0.328*	-0.396*
	Block 3 (enter)	**Depression severity**	0.145	0.038	0.198	0.031
	Block 4 (enter)	**Early life stress**	0.273	0.128		**0.400***
HDL cholesterol	Block 1 (forward)	No variable associated				
	Block 2 (forward)	No variable associated				
	Block 3 (enter)	**Depression severity**	0.156	0.156	**-0.395***	-0.280†
	Block 4 (enter)	**Early life stress**	0.243	0.088		**-0.317***
LDL cholesterol	Block 1 (forward)	Age	0.151	0.151	0.388*	0.392**
	Block 2 (forward)	Physical exercise	0.318	0.167	-0.409**	-0.453**
	Block 3 (enter)	**Depression severity**	0.327	0.009	-0.096	-0.134
	Block 4 (enter)	**Early life stress**	0.333	0.007		0.092
LDL-C/HDL-C	Block 1 (forward)	No variable associated				
	Block 2 (forward)	Physical exercise	0.129	0.129	-0.359*	-0.391*
	Block 3 (enter)	**Depression severity**	0.177	0.048	0.223	0.104
	Block 4 (enter)	**Early life stress**	0.242	0.065		0.286†
TC/HDL-C	Block 1 (forward)	No variable associated				
	Block 2 (forward)	Physical exercise	0.126	0.126	-0.355*	-0.394*
	Block 3 (enter)	**Depression severity**	0.181	0.055	0.240	0.104
	Block 4 (enter)	**Early life stress**	0.266	0.085		**0.326***

Input variables: Block 1: demographic variables (age, gender, and years of education); Block 2: lifestyle variables (body mass index and physical exercise per week); Block 3: depression severity (BDI score); Block 4: early life stress (CTQ total score). Bold values indicate the significant differences related to depression severity and ELS. † $P<0.1$, * $P<0.05$, ** $P<0.01$. β, standardized beta coefficient at the current step; β', standardized beta coefficient in the final model; BDI, Beck Depression Inventory; CTQ, Childhood Trauma Questionnaire-Short Form; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDD; major depressive disorder; TC, total cholesterol.

2.4.2.4. The relationship between the different subtypes of ELS and serum lipid/lipoprotein levels

Within the entire MDD group, additional series of hierarchical linear regressions were calculated to determine which subtypes of childhood adversities can significantly predict the parameters of the lipid profile as dependent variables after controlling for demographic variables (Block 1), lifestyle variables (Block 2), and depression severity (BDI score; Block 3) with the Forward variable selection method. In Block 4, the CTQ subscores of the different trauma types, as predictor variables of main interest, were added to the models using the Enter procedure.

As it is shown in Table 3, we found significant negative associations between physical neglect and abuse and between HDL-C. We also found significant positive associations between physical and emotional neglect and abuse, and the levels of triglycerides. Moreover, significant positive associations were found between physical and emotional neglect and the indices of LDL-C/HDL-C and TC/HDL-C. Sexual abuse had no statistically significant relationship between any of the lipid parameters (Table 3).

TABLE 3. Linear regression analyses with serum lipid and lipoprotein levels as dependent variables, and with trauma types (CTQ subscores) as predictors in the entire MDD group.

	Total cholesterol[a]		Triglycerides[b]		HDL cholesterol[c]		LDL cholesterol[d]		LDL-C/HDL-C[b]		TC/HDL-C[b]	
	β	***P***	**β**	***P***	**β**	***P***	**β**	***P***	**β**	***P***	**β**	***P***
CTQ physical neglect	0.150	0.277	**0.351**	**0.017**	**-0.306**	**0.034**	0.179	0.182	**0.392**	**0.006**	**0.403**	**0.005**
CTQ physical abuse	-0.166	0.231	**0.320**	**0.031**	**-0.304**	**0.037**	-0.089	0.516	0.200	0.180	0.197	0.187
CTQ emotional neglect	0.176	0.198	**0.381**	**0.010**	-0.200	0.188	0.194	0.148	**0.358**	**0.014**	**0.419**	**0.004**
CTQ emotional abuse	-0.087	0.529	**0.308**	**0.041**	-0.291	0.054	0.008	0.956	0.223	0.138	0.248	0.099
CTQ sexual abuse	-0.240	0.083	0.114	0.463	0.050	0.764	-0.195	0.169	0.003	0.984	0.045	0.772

Statistically significant results are presented in bold. [a] Adjusted for age and body mass index. [b] Adjusted for physical exercise per week. [c] Adjusted for depression severity. [d] Adjusted for age and physical exercise per week. CTQ, Childhood Trauma Questionnaire-Short Form; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDD, major depressive disorder; TC, total cholesterol.

2.4.3. Neurocognition

2.4.3.1. Two-group comparisons: healthy controls versus the entire MDD group

One-way ANOVA revealed significant group differences when we compared omission errors of the Conners' Continuous Performance Test (Welch's $F_{(1,58.5)}$=7.464, P=0.008, Cohen's d=0.75). Similarly, one-way ANOVA revealed significant group differences when we compared perseverative errors of the Wisconsin Card Sorting Test (Welch's $F_{(1,50.8)}$=5.463, P=0.023, Cohen's d=0.63) (for details, see Supplementary Table 2). After controlling by ANCOVA for age, gender, and level of education, however, these differences lost their significance (Supplementary Table 3).

2.4.3.2. Three-group comparisons: healthy controls versus MDD Only versus MDD+ELS

The ANOVA omnibus tests revealed that omission errors of the Conners' Continuous Performance Test were significantly different in the three groups (Welch's $F_{(2,36.6)}$=3.780, P=0.032, Cohen's d=0.64). Further comparison with the Games-Howell post-hoc test revealed that the CPT omission errors were significantly higher in the MDD+ELS group than in the HC (P=0.045, Cohen's d=0.65) (for details, see Supplementary Table 2). However, after controlling for the effects of demographic variables, no significant between-group differences were found in the neurocognitive variables (Supplementary Table 3).

2.4.3.3. The effect of serum lipid/lipoprotein levels on neurocognitive performances in MDD

Finally, hierarchical multiple linear regressions were calculated to predict parameters of neurocognitive tests based on lipid parameters after controlling for demographic variables (Block 1), lifestyle variables (Block 2), the severity of depression (BDI score; Block 3), and severity of ELS (CTQ total score; Block 4) that were included in the regression models with the Forward procedure. The lipid profile elements, as predictor variables of main interest, were added to the models using the Enter method in Block 5.

Depression severity predicted commission errors in the Conners' Continuous Performance Test (β=0.289, P=0.024) and detectability (β=-0.304, P=0.020), as well as

conceptual level responses in the Wisconsin Card Sorting Test (β=-0,416, P=0.006) in Block 3. For these significant associations between depression severity and cognitive performances, Cohen's f^2 values ranged from 0.15 to 0.20 suggesting moderate effect sizes. However, we could not find any association between the amount of ELS and any of the neurocognitive test results in Block 4. No relationship was found between lipid parameters and any of the Conners' Continuous Performance Test results. However, we could detect significant negative associations between the lipid profiles and between specific domains of the Wisconsin Card Sorting Test. There were significant negative associations between HDL-C and WCST perseverative errors, between LDL-C/HDL-C ratio and WCST total correct responses, and also between the indices LDL-C/HDL-C and TC/HDL-C, and WCST conceptual level responses (Table 4). Cohen's f^2 values for these results ranged from 0.10 to 0.16 suggesting moderate effect sizes.

TABLE 4. Linear regression analyses of serum lipid and lipoprotein levels as predictors of executive functioning (WCST scores) in the entire MDD group.

	WCST total correct responses		**WCST perseverative errors[a]**		**WCST non-perseverative errors[b]**		**WCST conceptual level responses[c]**	
	β	***P***	**β**	***P***	**β**	***P***	**β**	***P***
Total cholesterol	-0.130	0.411	-0.088	0.532	-0.038	0.794	-0.153	0.292
Triglycerides	-0.235	0.134	0.219	0.100	0.062	0.673	-0.266	0.074
HDL cholesterol	0.167	0.290	**-0.283**	**0.027**	-0.167	0.255	0.192	0.224
LDL cholesterol	-0.236	0.133	-0.068	0.629	-0.036	0.806	-0.241	0.093
LDL-C/HDL-C	**-0.306**	**0.048**	0.151	0.251	0.105	0.471	**-0.340**	**0.022**
TC/HDL-C	-0.252	0.108	0.193	0.139	0.146	0.318	**-0.309**	**0.039**

Statistically significant results are presented in bold. [a] Adjusted for age and education. [b] Adjusted for education. [c] Adjusted for depression severity. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDD; major depressive disorder; TC, total cholesterol; WCST, Wisconsin Card Sorting Test.

2.5. Discussion

The principal aim of the present study was to examine the impact of early life stress on serum lipid profiles in depressed patients. In our statistical analysis, we asked the question of whether depression severity or the severity of adverse childhood experiences have a stronger influence in determining serum lipid levels. Overall, ELS was a stronger predictor of serum lipid profiles than depression severity. Furthermore, we found that depressed patients with ELS had significantly higher serum triglyceride and lower HDL-cholesterol concentrations compared to MDD patients without ELS. The atherogenic indices, LDL-C/HDL-C, and TC/HDL-C were also higher in patients with ELS. We also found significant associations between the different ELS types and lipid profiles. Both physical and emotional neglect and abuse had a significant positive association with serum triglyceride levels, while physical neglect and abuse had a significant negative association with HDL-cholesterol. Finally, we could detect significant associations between depression severity and specific domains of the cognitive tests as well as between lipid profiles and certain results of the Wisconsin Card Sorting Test. But in our study, ELS did not influence the cognitive performance of the subjects.

2.5.1. The relationship between early life stress and serum lipid profiles in major depressed patients

A vast number of studies report that early life adversity may increase cardiovascular risk factors and the occurrence of CVD (see e.g., Batten et al., 2004; Dong et al., 2004; Goodwin and Stein, 2004; Danese et al., 2009; Fuller-Thomson et al., 2010, 2012; Korkeila et al., 2010; Stein et al., 2010; Scott et al., 2011; Rich-Edwards et al., 2012; Basu et al., 2017; Murphy et al., 2017; Reid et al., 2018; Obi et al., 2019; Doom et al., 2019). These studies document that childhood adversities are associated with hypertension (Danese et al., 2009; Stein et al., 2010; Reid et al., 2018; Doom et al., 2019), higher BMI (Doom et al., 2019), ischemic heart disease (Dong et al., 2004) and myocardial infarction (Fuller-Thomson et al., 2012). Adverse childhood experience may alter serum lipid/lipoprotein profiles as adults with ELS may have elevated serum triglycerides, LDL-cholesterol, and total cholesterol as well as low HDL-cholesterol (Danese et al., 2009; Spann et al., 2014; Reid et al., 2018; Doom et al., 2019). Furthermore, a recent study reported that the different trauma types can be associated with specific changes in serum levels, i.e., physical and sexual abuse were associated with high LDL-C and low HDL-C, and childhood neglect with raised

triglycerides and low HDL-C (Li et al., 2019). The exact physiological pathways connecting ELS with CVD risk factors and CVD are yet unknown. Recently, a hypothesis has been put forward that experiencing social threat and adversity up-regulates pro-inflammatory cytokines which in turn may elicit depressive symptoms as well as metabolic syndrome and cardiovascular disease (Slavich and Irwin, 2014).

A large body of evidence indicates that there is a strong association between MDD and CVD (Musselman et al., 1998; Penninx et al., 2001; Carney et al., 2002; Barth et al., 2004; Whooley, 2006; Van der Kooy et al., 2007; Goldstein et al., 2015). While the exact relationship between these two disorders remains obscure there is evidence that the presence of depressive symptoms can increase the risk of CVD (Joynt et al., 2003; Almeida et al., 2007; Vancampfort et al., 2014; Pérez-Piñar et al., 2016). Among the various CVD risk factors, dyslipidemia has also been associated with depressed mood (Huang et al., 2003; Papakostas et al., 2004; Chien et al., 2013; van Reedt Dortland et al., 2010, 2013). However, the studies investigating serum lipid concentration in MDD yielded inconsistent results. There are reports on higher (Ledochowski et al., 2003; Nakao et al., 2004; Moreira et al., 2017) as well as lower serum total cholesterol levels (Olusi et al., 1996; Maes et al., 1997; Ong et al., 2016) compared to controls, while others found no difference (Lehto et al., 2008; van Reedt Dortland et al., 2010; Enko et al., 2018). Other studies found that TG levels are increased in patients with MDD and that TG levels show a positive relationship with depression severity (Sevincok et al., 2001; Huang and Chen, 2004; Liu et al., 2016).

So far only a handful of studies examined the influence of ELS on lipid profiles in depressed patients. McIntyre and co-workers (2012) examined a clinical population with unipolar depression and found a significantly lower level of HDL-C in patients who experienced traumatic life events during their childhood compared to those without childhood adversities. However, there was no statistically significant difference in the overall rate of dyslipidemia and/or metabolic syndrome between subjects with and without childhood adversity. Wingenfeld and colleagues (2017) conducted a women-only study in a physically healthy clinical sample and detected no difference in triglycerides, cholesterol, HDL-C, LDL-C, and other metabolic risk markers between MDD patients with and without sexual or physical abuse. More recently Deschênes and co-workers (2018) reported that adverse childhood experiences are indirectly associated with diabetes via depressive symptoms and cardiometabolic dysregulations. The most recent study found decreased total cholesterol levels in adult outpatients with MDD with a childhood history of physical violence (Kraav et al., 2019). The same study found no differences in serum levels of HDL-

C and LDL-C between the groups (Kraav et al., 2019).

In our investigation, no differences could be detected between the entire MDD group and the healthy controls in any serum lipids and lipoproteins. These results are consistent with an extensive study carried out by van Reedt Dortland et al. (2010). In this study, involving 761 patients with current MDD and 629 HCs, the authors found that all significant differences between the MDD and healthy subjects in serum lipids/lipoproteins disappeared after adjustments for lifestyle factors, especially BMI. The authors, therefore, concluded that lipid alterations in MDD may be due to depression-related lifestyle characteristics rather than to depression itself. In our study, there were no significant differences in healthy controls' and MDD patients' lifestyle characteristics (including BMI and the amount of physical exercise.) Neither, the HC and the entire MDD group differed in the lipid profile. However, when we divided the MDD group into patients with and without a history of ELS, we found that TG, TC/HDL-C, and LDL-C/HDL-C significantly differed between the MDD+ELS and the HC groups, and TG, HDL-C, and TC/HDL-C were also significantly different between the MDD+ELS and the MDD Only groups after adjustments for age, gender, education, BMI and physical exercise. Furthermore, when we examined the possible associations between the severity of depressive symptoms (BDI score) and lipid/lipoprotein levels in the entire MDD group, we found a negative relationship only between BDI and the level of HDL-C, and no relationships with other lipids. This result is consistent with studies suggesting that compared to other lipids, low HDL-C level is specifically associated with depressive symptomatology (Maes et al., 1997; Chen et al., 2001; Lehto et al., 2008). However, when we also added the severity of ELS (CTQ total score) to the regression models, the relationship between BDI and HDL-C lost its significance. In contrast, the CTQ total score had a significant negative association with HDL-C level and a significant positive association with the serum level of TG and TC/HDL-C index.

Taken together, our present data suggest that ELS and not depressive psychopathology appears to be the primary determinant of lipid profile abnormalities in MDD. This result is independent of the way depression is operationalized (i.e., based on either the diagnosis of the MDD or the severity of depressive symptoms). Thus, serum lipid and lipoprotein alterations may be primarily characteristic of MDD patients who experienced high amounts of stress in their early lives rather than a feature of MDD in general.

We could also detect significant associations between the different ELS types and lipid profiles. Physical neglect and abuse had a significant negative association with HDL-cholesterol while physical and emotional neglect and physical and emotional abuse had a

significant positive association with serum triglyceride levels. Moreover, significant positive associations were found between physical and emotional neglect and the indices of LDL-C/HDL-C and TC/HDL-C. Our findings are in harmony with the recent study of Li and co-workers (2019), which reported that physical abuse was associated with low HDL-C, while neglect was associated with raised triglycerides and lower HDL-C. In our present study, we could not detect any association between sexual abuse and serum lipid/lipoprotein levels. Others found that sexual abuse was associated with high LDL-C and low HDL-C (Li et al., 2019). There is, in fact, ample evidence in the literature that childhood sexual abuse can increase the incidence of CVD: a US study involving 5 900 subjects reported that childhood sexual abuse was associated with increased risk of cardiac disease (Goodwin and Stein, 2004). Another US survey involving 12900 individuals found that specifically in men childhood sexual abuse was associated with a heart attack (Fuller-Thomson et al., 2012). One should add that there are negative findings as well, e.g., a recent retrospective study involving 3 600 individuals could not reveal any consistent association between the specific type of early psychosocial adversity and CVD risk factors (Anderson et al., 2018). This study examined associations of specific types of psychosocial adversities, such as lack of maternal care, maternal overprotection, parental mental illness, household dysfunction, sexual abuse, physical and emotional abuse, and neglect in childhood with CVD risk factors including BMI, triglycerides, low and high-density lipoprotein cholesterol (Anderson et al., 2018).

2.5.2. Factors influencing cognitive functioning in major depressed patients

A vast body of work has linked early life adversity to various types of cognitive deficits later in life (see e.g., Evans and Schamberg, 2009; Mueller et al., 2010; Pechtel and Pizzagalli, 2011; Gould et al., 2012; Chen and Baram, 2016). Cognitive impairments are also frequently present in depressed individuals (Porter et al., 2003; Marazziti et al., 2010; Ahern and Semkovska, 2018). A meta-analysis found significant cognitive deficits in executive function, memory, and attention in depressed patients relative to controls (Rock et al., 2014), yet another one revealed significant correlations between depression severity and specific domains of episodic memory, executive function, and processing speed (McDermott and Ebmeier, 2009). In our present study, we could also detect significant associations between depression severity and specific domains of attention (examined with the Conners' Continuous Performance Test-II) and executive functions (investigated with the Wisconsin Card Sorting Test). However, we could not find any association between ELS and cognitive

performance using these two tests.

Numerous clinical and preclinical data suggest that dyslipidemia can be linked to cognitive deficits and decline (Yaffe et al., 2002; Farr et al., 2008; Gendle et al., 2008; Morley and Banks, 2010; Reynolds et al., 2010) though this issue is not without controversies (see e.g., Panza et al., 2006; Anstey et al., 2008). For example, there are reports that high triglycerides are associated with poor memory and general cognitive decline (de Frias et al., 2007; Morley and Banks, 2010), and that high triglyceride levels inversely correlate with executive function in non-demented elderly adults (Parthasarathy et al., 2017). Furthermore, a recent study documented elevated triglyceride levels in patients with MDD, which was associated with cognitive impairments (Shao et al., 2017). In our study, we found negative associations between lipid profiles (HDL-C and LDL-C/HDL-C, TC/HDL-C ratios), and specific domains of the Wisconsin Card Sorting Test measuring executive functions. Low levels of HDL cholesterol have been associated with poor memory (Singh-Manoux et al., 2008; Feinkohl et al., 2019), impaired executive functions (Sun et al., 2019) and cognitive decline (van Exel et al., 2002), as well as with lower gray matter volumes (Ward et al., 2010). It should be added here that higher levels of HDL-C have been associated with a decreased risk of Alzheimer's disease (Reitz et al., 2010) and that low HDL-C levels can result in cerebral amyloidosis (Reed et al., 2014).

2.5.3. Limitations

The low sample size is a major limitation of this study. A further important limitation is that we used a retrospective self-report to assess ELS. Ideally, the long-term effects of childhood adversities should be studied in prospective longitudinal studies, and using qualitative or mixed methods can also add further valuable information when studying the impact of experienced traumas (see e.g., Boeije et al., 2013; Esposito et al., 2019), especially because self-reports can be biased. For example, social desirability can be an important potential bias when reporting past traumatic events especially in health-related research (see e.g., Adams et al., 2005; van de Mortel, 2008; Caputo, 2017 on this topic). Another limitation of our study design is that it does not allow us to derive causal relations, but only associations. To compensate for these limitations we did our best to carefully select the participants and match them in age, gender, lifestyle habits, and clinical data. Notably, only a few studies (Ding et al., 2014; Wingenfeld et al., 2017) included a control group in their studies, besides the MDD patients with or without ELS. We also carefully analyzed the

influence of the various ELS subtypes. Finally, we also assessed the cognitive performance of our subjects and none of the earlier studies did such measurements.

3. Theory of mind disturbances in borderline personality disorder: a meta-analysis

3.1. Introduction

Borderline personality disorder (BPD) is a phenomenologically heterogeneous disorder characterized by affective, cognitive, behavioral, and interpersonal (i.e., disturbed relatedness) symptom areas (APA, 2013). It is widely accepted that BPD patients' unstable relational style is of central importance (Gunderson, 2007), and other symptoms, such as impulsivity, self-harm, anger, or emotional instability are consequences of or triggered by the social, interpersonal context (Kehrer and Linehan, 1996; Brodsky et al., 2006; Hepp et al., 2017). Clinical research has paid increasing attention to BPD patients' social dysfunctions during the past decades, and a growing body of data indicates that BPD patients have social-cognitive deficits (Daros et al., 2013; reviewed by Dinsdale and Crespi, 2013; Roepke et al., 2013; Lazarus et al., 2014). Theory of mind (ToM) (or mentalizing) is one of the essential components of social cognition by which we can attribute mental states, such as beliefs, intentions, and emotions, to others (Baron-Cohen et al., 1985).

Hence, ToM is a multidimensional construct involving several dimensions. Sabbagh (2004) identified two processes of ToM: (1) *mental state decoding* is the social-perceptual aspect of ToM, which involves the ability to detect and discriminate others' mental states based on their observable social behavior; and (2) *mental state reasoning* implies the social-cognitive aspect, involving causal inferences and predictions about others' mental states based on additional information sources including context and general social knowledge. A further distinction can be made between components of ToM (Shamay-Tsoory et al., 2006): one component is involved in understanding others' intentions and beliefs (*cognitive,* or 'cold' ToM), whereas the other one processes other people's feelings and emotions (*affective,* or 'hot' ToM). The findings of the functional brain imaging studies sustain the separate neurological underpinnings of ToM decoding and reasoning, as well as those of cognitive and affective ToM (Sabbagh, 2004; Schlaffke et al., 2015). During the past years, increasing attention has been paid to the disassociations of processes and components of ToM in specific clinical populations. Several studies found intact or enhanced mental state decoding abilities together with a dissociation between decoding and reasoning abilities in BPD samples (Preißler et al., 2010; Baez et al., 2015; Zabihzadeh et al., 2017). Harari et al. (2010) found a dissociation between cognitive and affective ToM in patients with BPD, but this dissociation was not replicated in later studies (Baez et al, 2015; Petersen et al. 2016).

Recently, two studies using different ToM tasks in the same sample reported a decoupling of mental state decoding and reasoning abilities, as well as that of affective and cognitive ToM in BPD (Baez et al., 2015; Zabihzadeh et al., 2017).

Clinical studies report common comorbidities in the BPD populations: e.g., 41–83 % for major depressive disorder (MDD), 10–20% for bipolarity, 64–66% for substance misuse, 46–56% for post-traumatic stress disorder (PTSD), 23–47% for social phobia, 16–25% for obsessive-compulsive disorder, 31–48% for panic disorder, and 29–53% for any eating disorder (Zanarini et al., 1998; Lieb et al., 2004). Among these, PTSD has been found to negatively and MDD positively influence ToM performance in BPD patients (Preißler et al., 2010; Richman and Unoka, 2015; Unoka et al., 2015).

Until now, several studies have investigated ToM in BPD, but the results were controversial. Discrepant findings on ToM deficits in BPD might be caused by the low sample sizes, the variability of the ToM processes and components assessed, as well as the heterogeneity of the clinical samples mainly due to the comorbidities. To resolve controversies, we conducted a quantitative meta-analysis (MA) of the existing data on ToM in BPD. So far, two meta-analyses of social cognition in BPD have been published. Daros et al. (2013) reviewed and meta-analyzed data on facial emotion recognition in BPD – involving 10 primary studies, while Richman and Unoka (2015) aggregated and meta-analyzed ToM results of 5 studies. However, the latter publication comprised only studies using the Reading the Mind in the Eyes Test (RMET; Baron-Cohen et al., 2001) to assess ToM in BPD.

3.2. Objectives

This study used meta-analytic methods to characterize BPD patients' ToM abilities and to investigate the confounding factors behind the conflicting results of the literature. We hypothesized that BPD patients could be characterized by a specific social-cognitive profile, i.e. we expected to find specific alterations for different processes and subcomponents of ToM in BPD. Based on the literature, we further hypothesized that the various ToM tests are differentially sensitive to ToM deficits in BPD due to their psychometric and thematic features. Therefore, a series of meta-analyses were designed for separately assessing mental state decoding and reasoning abilities, affective and cognitive ToM performances, and the performances in different types of ToM tests. Finally, a series of meta-regression analyses were planned to examine the impact of demographic variables and psychiatric comorbidities

on ToM capacities of BPD patients.

3.3. Methods

3.3.1. Literature search and study selection

PRISMA guideline (Moher et al., 2009) was followed when conducting this MA. In agreement with other meta-analyses on ToM deficits in psychiatric disorders (recently reviewed by Cotter et al., 2018), electronic, peer-reviewed databases including PubMed, Scopus, PsycINFO, and Web of Science (from January 1990 to November 2017) were searched using keywords {"Theory of mind" OR "mentalizing" OR "social cognition"}, AND {"borderline personality disorder"}. The reference list of papers examined for eligibility criteria, as well as that of reviews on social cognition in BPD, were also checked for additional publications.

The initial search strategy yielded 697 studies. After filtering duplicates, 445 studies were screened for eligibility criteria. Studies were selected if they (1) investigated ToM performances of patients with BPD fulfilling DSM-IV criteria confirmed by the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II, First et al., 1997) (2) included healthy comparison groups, (3) used well-established, valid, and widely used ToM tests, and (4) presented appropriate data to determine effect sizes and variances. All identified publications were reviewed and data were extracted by two authors independently. Inconsistencies of study selection and data extraction were discussed. A discrepancy of data extraction appeared with regard to one publication (5%); nonetheless, it was resolvable: after discussion, there was a 100% agreement on data extraction.

Reasons for exclusion were: participants with no or with not sufficiently established diagnosis of BPD (n=4), no healthy comparison group (n=4), no eligible ToM tasks (n=3), overlapping sample (n=1), mixed clinical sample (n=2). We did not include studies with adolescent samples (n=4), because ToM skills are known to be developing during that age (Blakemore, 2008); therefore, adding adolescent samples to the MA with adults would substantially increase the heterogeneity. Regarding the commonly co-occurring psychiatric comorbidities in BPD, samples with typical psychiatric comorbidities (e.g., MDD, PTSD, eating disorders, anxiety disorders, and other personality disorders) were not excluded from the meta-analysis. Figure 2 presents a flowchart of the study selection process. We also contacted authors for unreported data and missing information.

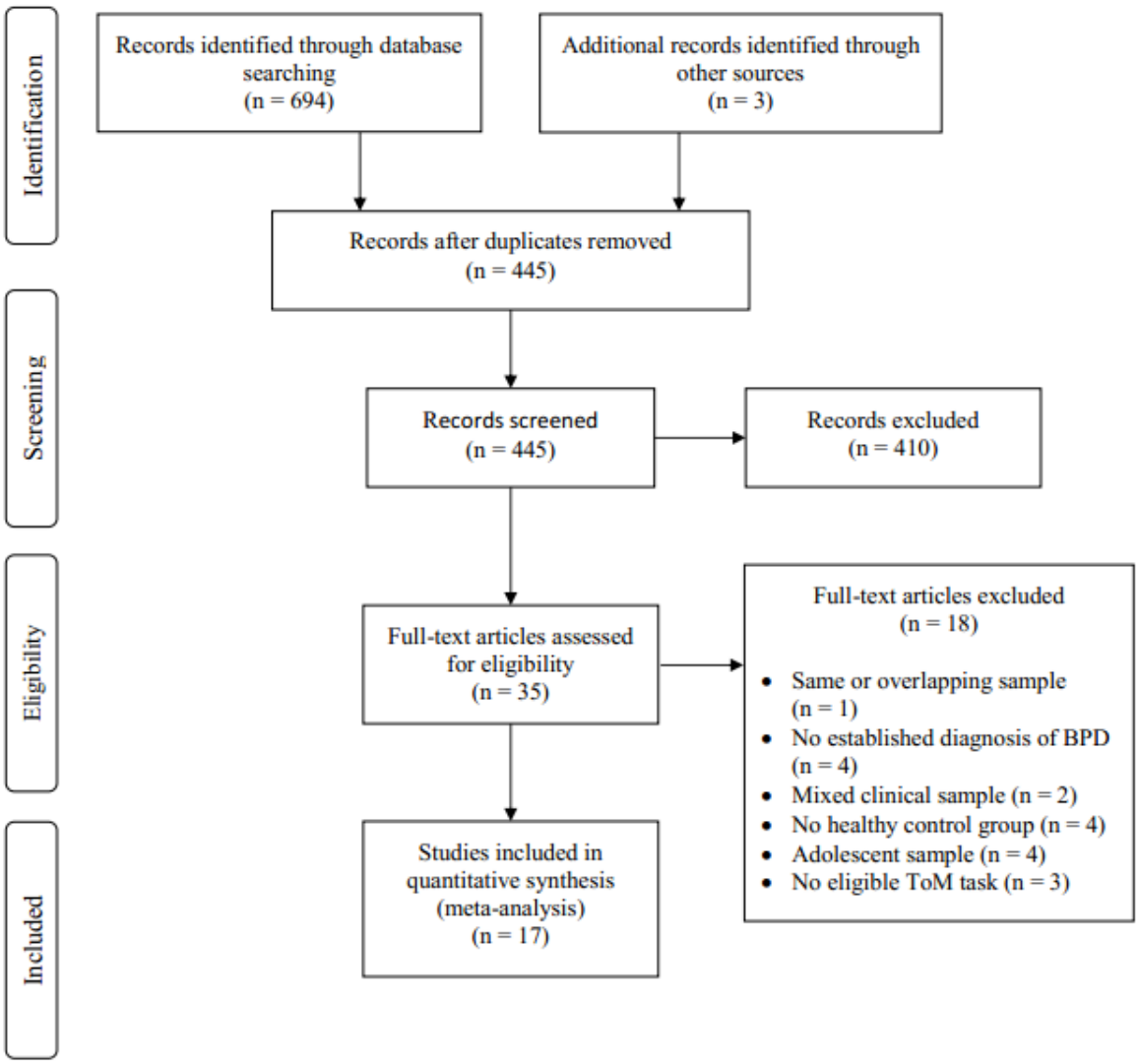

FIGURE 2. Flowchart of the study selection process.

Seventeen studies involving 585 patients with BPD, as well as 501 healthy controls (HC) passed the inclusion criteria (Table 5). There was no significant between-group difference for age (*d*=-0.06, 95% *CI*=-0.18 to 0.06, *Z*=-0.97, *P*=0.33). The percentage of males was higher in the HC groups (11.99%) than in the BPD groups (9.2%), and there was a significant difference for gender between BPD and HC across the studies (*RR*=1.18, 95% *CI*=1.04 to 1.35, *Z*=2.49, *P*<0.05). Therefore, gender was added as a moderator to the analysis.

TABLE 5. Characteristics of included studies.

Study	Sample (female) BPD – HC	Matched for	ToM tasks	Characteristics of BPD group				Outcome
				Mean age	MDD % *(lifetime)*	PTSD %	Medication status	
Arntz et al. (2009)	16(16) – 28(28)	Age, gender, IQ	ATT	30.5	–	–	–	No difference
Fertuck et al. (2009)	30(26) – 25(15)	Age, edu	RMET	29.8	56.7 *(76.7)*	30	13.3%	BPD > HC
Harari et al. (2010)	20(18) – 22(19)	Age, edu, gender, IQ	FPT	32.1	0	0	–	FP recognition, cognitive FP: BPD < HC, affective FP: no difference
Ghiassi et al. (2010)	50(46) – 20(13)	Age	MSAT	26.2	–	–	majority of the sample	No difference
Preißler et al. (2010)	64(64) – 38(38)	Age, gender, IQ	MASC, RMET	29.2	12.5 *(42.2)*	35.9	32.8%	MASC: BPD < HC RMET: no difference
Dziobek et al. (2011)	21(21) – 21(21)	Age, gender, IQ	MET	31.7	19 *(28.6)*	38.1	–	Cognitive empathy score: BPD < HC
Schilling et al. (2012)	31(30) – 27 (12)	Age, edu	RMET	27.3	67.7	16.1	80.6%	No difference
Frick et al. (2012)	21(21) – 20(20)	Age, edu, gender	RMET	21.7	23.8 *(47.6)*	33.3	0%	BPD > HC
Wingenfeld et al. (2014)	38(38) – 35(35)	Age, gender	MASC, MET	24.3	23.7	13.2	0%	No difference
Unoka et al. (2015)	78(74) – 76(69)	Age, edu, gender	RMET	29.9	43.6	5.1	majority of the sample	BPD < HC
Vaskinn et al. (2015)	25(25) – 25(25)	Age, edu, gender	MASC	30.7	52	12	–	No difference in overall score (Overmentalizing errors: BPD > HC)
Baez et al. (2015)	15(12) – 15(13)	Age, edu, gender	FPT, RMET	38.4	26.7	–	–	FP: BPD < HC RMET: no difference
Andreou et al. (2015)	44(38) – 38(22)	Age	MASC	29	61,4	0	–	Overmentalizing errors: BPD > HC Undermentalizing errors: no difference
Petersen et al. (2016)	19(18) – 20(19)	Age, gender, IQ	RMET, JAT, FPT, EAT, FBPST	32.5	0	52	94.7%	BPD < HC only in more complex tasks (FPT, JAT)
Brüne et al. (2016)	30(30) – 30(30)	Age, edu, gender	CAMS	25.7	–	–	63.3%	BPD < HC
Yeh et al. (2017)	40(37) – 36(33)	Age, edu, gender	FPT, ATT, NTT, TASIT	30.9	–	–	–	NTT, TASIT: BPD < HC ATT, FPT: no difference
Zabihzadeh et al. (2017)	44(21) – 25(12)	Age, edu, gender, IQ	RMET, FPT	26.2	50	34.1	–	RMET: BPD only > BPD+MDD > HC FPT: HC > BPD only > BPD+MDD

ATT, Advanced Theory of Mind Test; BPD, patients with borderline personality disorder; CAMS, Cartoon-Based Assessment of Mentalizing Skills; EAT, Expression Attribution Test; Edu, educational level; FBPST, False-Belief Picture Sequencing Task; FPT, Faux Pas Test; HC, healthy controls; JAT, Joke-Appreciation Task; MASC, Movie for the Assessment of Social Cognition; MDD, major depressive disorder; MET, Multifaceted Empathy Test; MSAT, Mental State Attribution Task; NTT, Nonverbal ToM Task; PTSD, post-traumatic stress disorder; RMET, Reading the Mind in the Eyes Test; TASIT, The Awareness of Social Inference Test; ToM, theory of mind.

3.3.2. Theory of mind measures

The most frequently applied ToM task was the Reading the Mind in the Eyes Test (RMET; Baron-Cohen et al., 2001) that measures the ability of mental state decoding (*n*=8). In the RMET, a series of photos presenting only the eye region of faces are shown, and participants are instructed to pick one from four words presented simultaneously with the eyes to best describe the emotional state of the person in the photo. However, partially based on neuroimaging studies, where RMET has been found to be related to amygdala activation (e.g., Russell et al., 2009), it is widely used as a measure of affective ToM as well.

Other tasks assessed the mental state reasoning abilities: Faux Pas Task (FTP; Stone et al., 1998) was used in 5 studies; in 2 other studies, ToM was measured with Happé's Advanced Theory of Mind Test (ATT; Happé, 1994). In addition, several ToM cartoons, the Multifaceted Empathy Test (MET; Dziobek et al., 2008), as well as the Movie for the Assessment of Social Cognition (MASC; Dziobek et al., 2006), which is an ecologically valid, video-based ToM task, and an another video-based ToM test, the Awareness of Social Inference Test (TASIT; McDonald et al., 2003) was applied in the selected studies for measuring mental state reasoning.

For subsequent subgroup analysis, we divided the existing ToM dataset into cognitive and affective ToM data. It is widely accepted in ToM research that specific ToM tests (or their subscores) are considered as measures of affective or cognitive ToM. There is an agreement in the literature that RMET predominantly measures the capacity to understand others' emotions and feelings (e.g., Petersen et al, 2016; Zabihzadeh et al., 2017), while false belief tests or ATT assess the capacity to understand others' beliefs and intentions. However, some more complex ToM tests (e.g., FPT, MASC, CAMS) contain separate questions for affective as well as cognitive ToM. In the case of the latter tests, if data were available, we calculated the cognitive and affective scores separately. Table 6 presents the complete list of ToM tasks and their categorization according to different task types and ToM components.

TABLE 6. List of ToM (theory of mind) tasks and their categorization according to different task types and ToM components.

ToM tasks	Study *N*	Task type	ToM processes	ToM contents
Advanced Theory of Mind Test (ATT) (Happé, 1994)	2	Verbal stories	Reasoning	Cognitive
Cartoon-Based Assessment of Mentalizing Skills (CAMS) (Dimaggio and Brüne, 2010)	1	Cartoons	Reasoning	Affective and cognitive
Expression Attribution Test (EAT) (Langdon et al., 2006)	1	Cartoons	Reasoning	Affective
False-Belief Picture Sequencing Task (FBPST) (Langdon and Coltheart, 1999)	1	Cartoons	Reasoning	Cognitive
Faux Pas Test (FPT) (Stone et al, 1998)	5	Verbal stories	Reasoning	Affective and cognitive
Joke-Appreciation Task (JAT) (Langdon et al., 2010)	1	Cartoons	Reasoning	Cognitive
Mental State Attribution Task (MSAT**)** (Brüne, 2005)	1	Cartoons	Reasoning	Cognitive
Movie for the Assessment of Social Cognition (MASC) (Dziobek et al., 2006)	4	Videos	Reasoning	Affective and cognitive
Multifaceted Empathy Test (MET) (Dziobek et al., 2008)	2	Pictures	Reasoning	Affective
Nonverbal ToM Task (NTT) (Yeh et al., 2009)	1	Cartoons	Reasoning	Cognitive
Reading the Mind in the Eyes Test (RMET) (Baron-Cohen et al., 2001)	8	Pictures	Decoding	Affective
The Awareness of Social Inference Test (TASIT) (McDonald et al., 2003)	1	Videos	Reasoning	Affective and cognitive

3.3.3. Statistical analysis

We conducted a meta-analysis on the results from the different studies using an aggregate data approach. Negative effect sizes indicated the poorer performance of the BPD group relative to the healthy group. For studies that reported more than one ToM task, within-study effect sizes, and variances were aggregated by the Gleser and Olkin (1994) procedure. Meta-analysis for overall ToM was conducted using aggregated effect sizes across all studies.

We performed separate categorical random-effects meta-analyses for the two main ToM processes: for mental state decoding (i.e., RMET only), and mental state reasoning (any other ToM task used in the studies). Effect sizes for the different valences of RMET (neutral, positive, negative) were also counted.

Subsequently, meta-analyses of affective and cognitive ToM were performed. Then, MAs for predominantly verbal, visual, and multimodal ToM tasks were conducted. If there were at least 4 studies reporting data on a particular task, then a separate, task-specific MA was also conducted (Fu et al., 2011). An individual task analysis was possible for FPT (n=5). Also, effect sizes for RMET (n=8, as mental state decoding), cartoons (contents differ; n=4), as well as for MASC (n=4) were calculated.

All statistical analyses were performed in R environment (R Development Core Team, 2015) with the Metafor (Viechtbauer, 2010) and the MAd packages (Del Re and Hoyt, 2014). Effect sizes were weighted using the inverse variance method. Because studies in the MA are not supposed to share a common effect size, the random-effects model with DerSimonian–Laird estimate was used to calculate summary effect sizes (DerSimonian and Laird, 1986). The homogeneity of the distribution of the weighted effect sizes was examined with the Q and I^2 tests (Hedges and Olkin, 2014). Between-study heterogeneity in the random-effects model was estimated with tau-squared (τ^2), an estimate of the total amount of heterogeneity

Publication bias was estimated with the Fail-Safe N test, and tests for assessing funnel plot asymmetry. Fail-Safe N test computes a pooled P-value for all studies in the MA and calculates how many further studies with a zero effect would be necessary to generate a non-significant P. Egger's test and Begg and Mazumdar's test rely on the assumption that studies with small sample sizes are more often published if they report significant results, while studies with large sample sizes are usually published regardless of significant findings.

Meta-regression analyses were conducted for age, gender (the ratio of females in the BPD group compared to that in the HC group), and education (years), as well as for clinical comorbidities (current MDD, anxiety disorders [= panic disorder + phobias + generalized anxiety disorder], social phobia, PTSD, any eating disorder, and substance use disorder). Table 7 presents the demographic and clinical characteristics of patients with BPD added as moderators to the meta-regression analyses. Other personality disorders, symptom severity of current depression, childhood trauma, and neurocognitive functions were also considered, but there were no sufficient data available to add them to the analysis. In the moderator analyses, we used study-level measures only when they were published in at least 7 studies (Fu et al., 2011). Categorical subgroup variables were used only when each subgroup had a minimum of 4 studies (Fu et al., 2011). For continuous moderators, analyses with a linear mixed-effects model, for categorical variables, subgroup analyses were conducted. Q_{bet}-test was used to compare the effect sizes of the subgroups (Borenstein et al., 2011).

TABLE 7. Demographic and clinical characteristics of patients with BPD that were added as moderators to the meta-regression analyses.

Moderators	Mean	SE	Study *N*
Age of BPD	29.5	0.81	17
Years of education	13.39	0.63	8
Ratio of females in the BPD versus that in the HC[a]	1	1-1.23	17
% of current MDE	37.33	6.99	14
% of anxiety disorders[b]	52.41	17.13	9
% of social phobia	16.68	6.11	9
% of PTSD	24.10	4.83	13
% of any ED	15.73	4.43	11
% of current SUD	12.93	3.5	11

[a] Risk ratio of BPD females; median and 25-75 percentile range are presented (instead of mean and SE). [b] Summed rate of DSM-5 anxiety disorders (panic disorder, agoraphobia, social anxiety disorder, specific phobia, and generalized anxiety disorder). BPD, borderline personality disorder group; ED, eating disorder; HC, healthy control group; MDE, major depressive episode; PTSD, post-traumatic stress disorder; SUD, substance use disorder.

3.4. Results

The summary of the main meta-analysis results is presented in Figure 3 and Table 8. (Negative effect sizes indicate the poorer performance of the BPD group.)

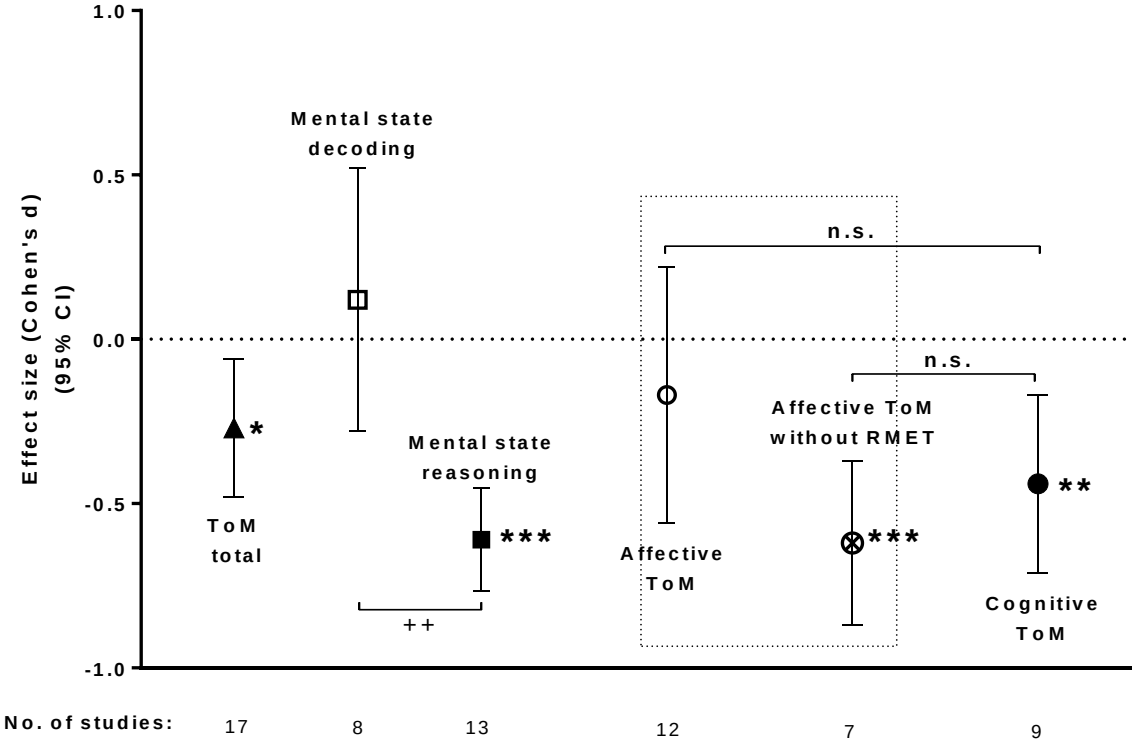

FIGURE 3. Summary of the main meta-analysis results.
Between-group effect sizes (Cohen's *d*s) for overall ToM (ToM total), mental state decoding and reasoning, as well as affective and cognitive ToM are presented. Bars represent the 95% confidence intervals. Negative effect size indicates the poorer performance of the BPD compared to HC. * $P<0.05$; ** $P<0.01$; *** $P<0.001$, BPD compared to HC. $^{++}$ $P<0.05$, Q_{bet}-test (comparisons of the effect sizes of the different ToM components).

TABLE 8. Mean weighted effect sizes for differences between patients with BPD and healthy controls on ToM.

ToM	St. *N*	BPD *N*	HC *N*	*d*	95% CI	*Z*	*P*	Q-test (*P*)	τ^2	Egger (*P*)	Begg (*P*)	Fail safe *N*
ToM Total	17	585	501	**-0.27**	-0.48, - 0.06	-2.56	**0.01**	< 0.001	0.13	0.09	0.09	134
ToM Processes												
Decoding (=RMET)	8	302	246	0.12	-0.28, 0.51	0.59	0.55	< 0.001	0.25	0.31	0.40	N.A.
Positive	7	287	231	-0.01	-0.43, 0.41	-0.04	0.97	< 0.01	0.26	0.34	0.38	N.A.
Neutral	7	287	231	-0.33	-0.97, 0.31	-1.01	0.31	< 0.001	0.66	0.96	0.77	N.A.
Negative	7	287	231	0.70	-0.06, 1.46	1.80	0.07	< 0.001	0.97	0.10	0.07	N.A.
Reasoning	13	425	353	**-0.61**	-0.87, -0.35	-4.60	**< 0.001**	< 0.001	0.16	0.62	0.59	244
ToM Contents												
Affective ToM	12	410	354	-0.17	-0.48, 0.15	-1.03	0.30	< 0.001	0.24	0.53	1.00	N.A.
Aff. ToM without RMET	7	206	181	**-0.62**	-0.87, -0.38	-4.95	**< 0.001**	0.18	0.04	0.09	0.24	57
Cognitive ToM	9	290	244	**-0.44**	-0.71, -0.17	-3.20	**0.001**	< 0.01	0.10	0.88	0.46	57
Task Types												
Visual	13	481	388	-0.14	-0.44, 0.16	-0.93	0.36	< 0.001	0.23	0.26	0.25	N.A.
RMET (=decoding)	8	302	246	0.12	-0.28, 0.51	0.59	0.55	< 0.001	0.25	0.31	0.40	N.A.
Cartoons	4	139	106	**-0.59**	-0.88, -0.31	-4.09	**< 0.001**	0.24	0.02	0.48	0.75	22
Verbal	6	154	146	**-0.81**	-1.46, -0.17	-2.48	**0.01**	< 0.001	0.55	0.49	0.72	55
Faux Pas Task	5	138	116	**-1.07**	-1.65, -0.50	-3.68	**< 0.001**	< 0.001	0.33	0.33	0.48	69
Videos	5	209	172	**-0.52**	-0.79, -0.25	-3.74	**< 0.001**	0.09	0.05	0.80	1.00	33
MASC	4	169	136	**-0.46**	-0.77, -015	-2.92	**< 0.01**	0.09	0.05	1.00	1.00	16

Statistically significant results are presented in bold. BPD, borderline personality disorder; HC, healthy controls; MASC, Movie for the Assessment of Social Cognition; RMET, Reading the Mind in the Eyes Test; ToM, theory of mind.

3.4.1. Overall theory of mind

Overall ToM performance (n=17) was significantly impaired in the BPD group compared with the HC group, but the effect size was small (d=-0.27, P=0.01) (Figure 4, Table 8). Because there was high heterogeneity for the distribution of effect sizes for the total ToM score, further moderator analyses were conducted. No publication bias was found.

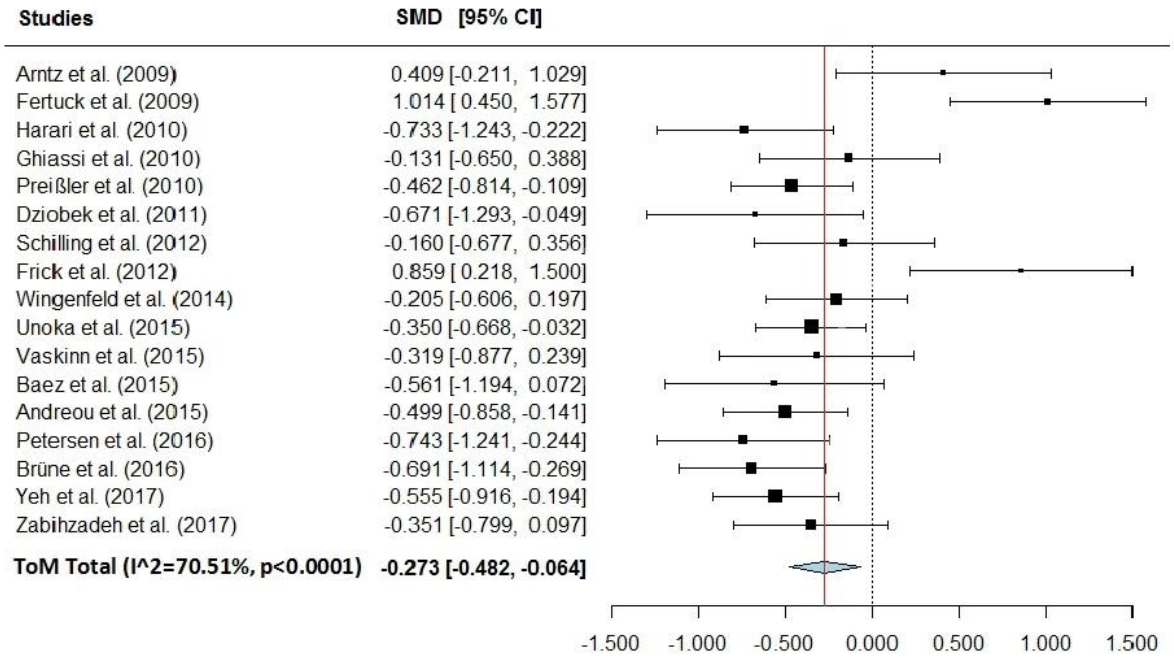

FIGURE 4. Forest plot for meta-analysis of overall ToM (theory of mind) in BPD (borderline personality disorder). Negative effect sizes indicate the poorer performance of the BPD group.

3.4.2. Mental state decoding versus mental state reasoning

Mental state decoding (separate analysis of RMET only; n=8): We found no significant effect size for overall accuracy in RMET (d=0.12, P=0.55). The distribution of the effect sizes was significantly heterogeneous (Figure 5, Table 8). Data on RMET were further analyzed for valence types (positive, negative, and neutral; n=7). Results showed no significant between-group differences for positive (d=-0.01), and for neutral valences (d=-0.33); heterogeneities were significant. Nevertheless, there was a trend level significant difference between BPD patients and HCs for the negative valence (d=0.70, P=0.07; heterogeneity was significant) (Table 8).

Mental state reasoning abilities were significantly impaired in BPD (d=-0.61, P<0.001, n=13) (Figure 6, Table 8).

BPD patients' mental state reasoning deficits were more robust compared to the mental state decoding abilities (Q_{bet}=9.89, P<0.05, n=13+8; Figure 3).

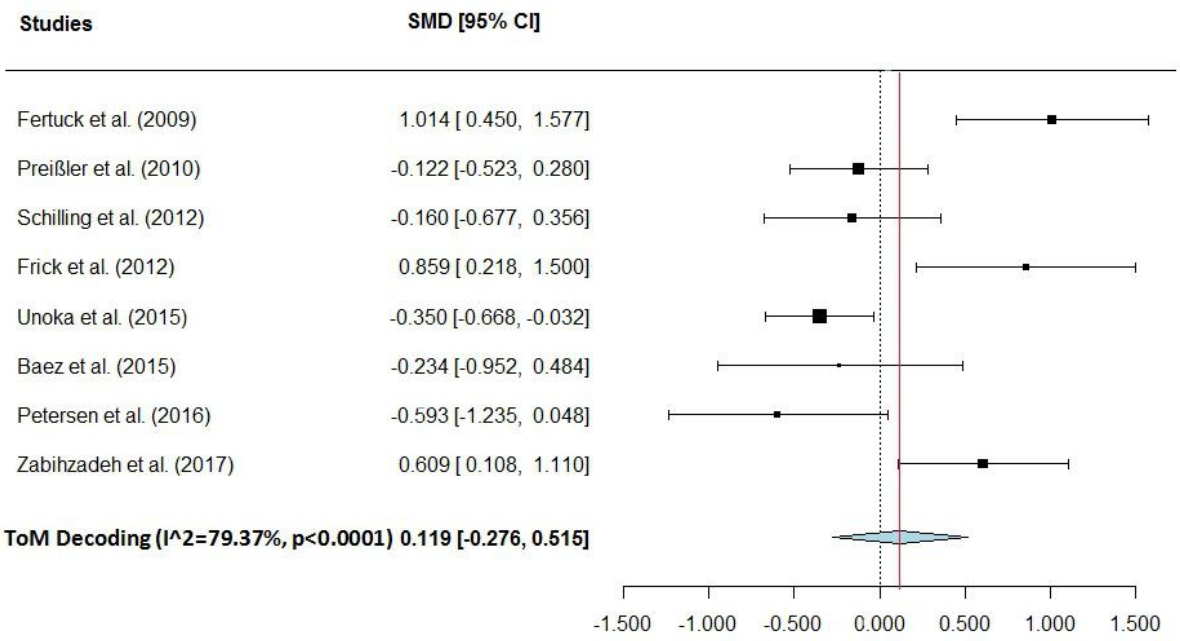

FIGURE 5. Forest plot for meta-analysis of mental state decoding in BPD (borderline personality disorder). Negative effect sizes indicate the poorer performance of the BPD group.

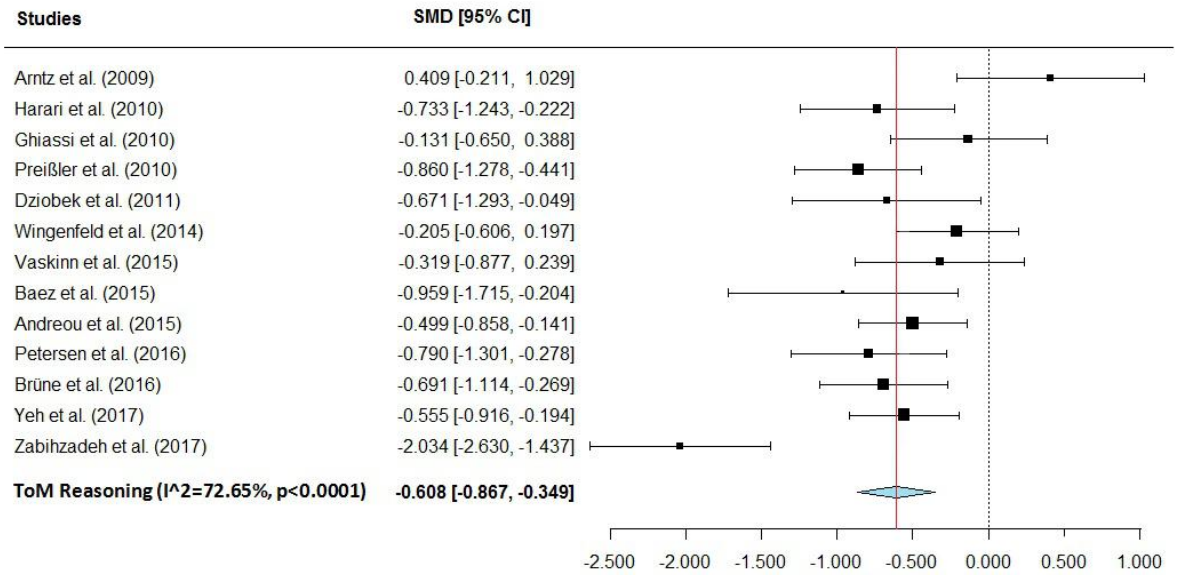

FIGURE 6. Forest plot for meta-analysis of mental state reasoning in BPD (borderline personality disorder). Negative effect sizes indicate the poorer performance of the BPD group.

3.4.3. Affective versus cognitive theory of mind

Affective ToM (*n*=12): Patients with BPD did not differ in their affective ToM abilities compared to HCs (*d*=-0.17, *P*=0.30) (Figure 7, Table 8). After removing RMET data from data on affective ToM, we calculated an effect size for the 'affective ToM without RMET' subgroup. Here, we found that BPD patients significantly underperformed HC in affective ToM tests (*d*=-0.62, *P*<0.001, *n*=7), if RMET data (i.e., data of affective decoding or discrimination) were removed from the subset of affective ToM data (Table 8).

Cognitive ToM (*n*=9): Patients with BPD performed significantly worse in cognitive ToM tasks (*d*=-0.44, *P*=0.001) (Figure 8, Table 8).

However, there was no significant difference between BPD patients' overall affective and cognitive ToM deficits (Q_{bet}=1.54, *P*=0.21, *n*=12+9.). Similarly, there was no significant difference between affective Tom without RMET and cognitive ToM (Q_{bet}=1.06, *P*=0.30, *n*=7+9; Figure 3).

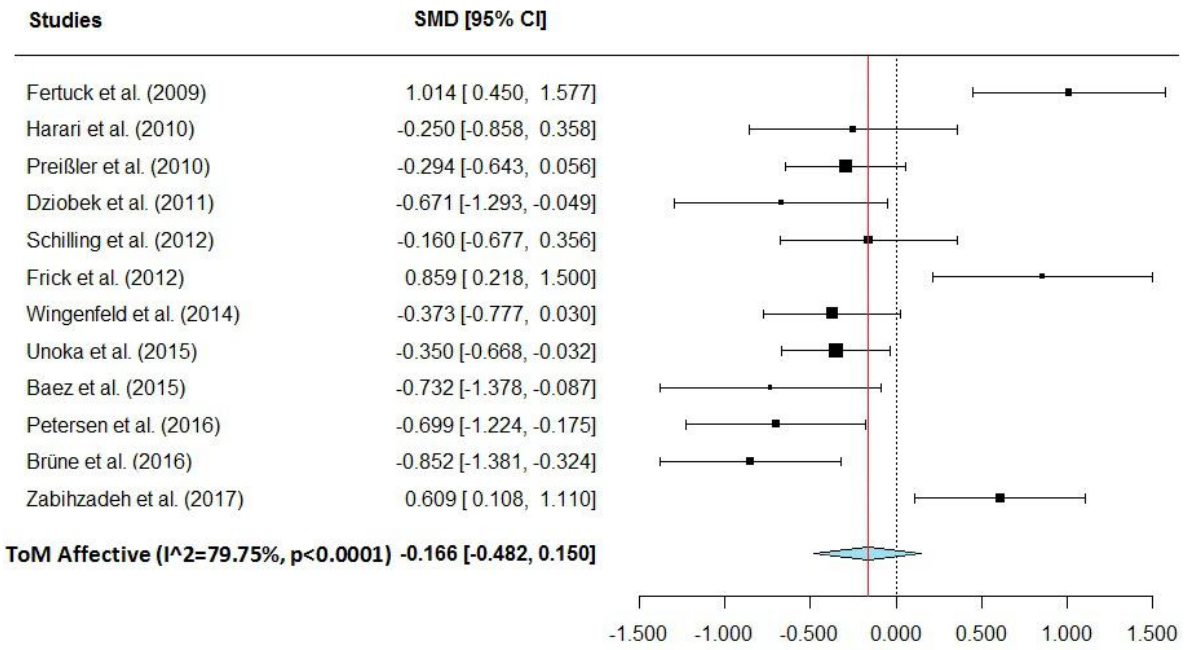

FIGURE 7. Forest plot for meta-analysis of affective ToM (theory of mind) in BPD (borderline personality disorder). Negative effect sizes indicate the poorer performance of the BPD group.

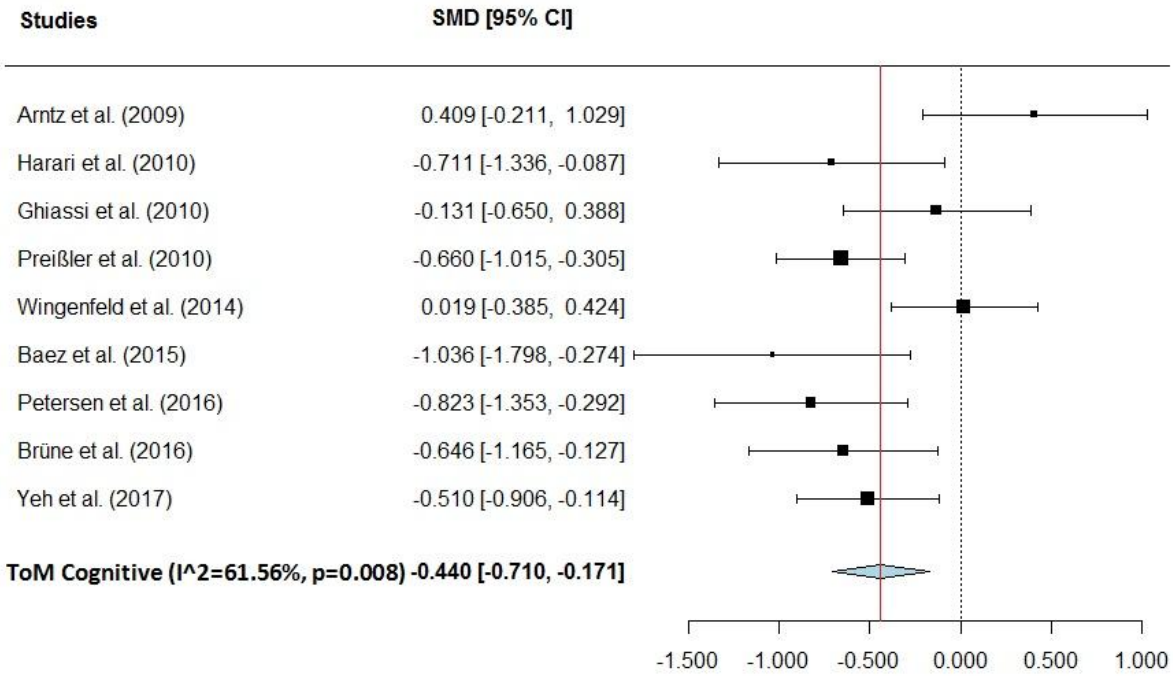

FIGURE 8. Forest plot for meta-analysis of cognitive ToM (theory of mind) in BPD (borderline personality disorder). Negative effect sizes indicate the poorer performance of the BPD group.

3.4.4. The effect of task types

We reanalysed data by task types, and calculated effect sizes for visual (d=-0.14, P=0.36, n=13), verbal (d=-0.81, P=0.01, n=6), and multimodal (i.e., video-based; d=-0.52, P<0.001, n=5) ToM tasks (Table 8). The comparison of performances in the three task types revealed that BPD patients performed significantly worse in verbal than in visual tasks (Q_{bet}=4.61, P<0.05).

To explore the origin of BPD patients' relatively good performance in visual tasks, we ran a separate MA with data of visual tests without RMET (i.e., cartoons and MET, n=6), and found a significant effect size: d=-0.54, P<0.001, 95% *CI*: -0.76 to -0.33, Z=-4.83, I^2= 16.34%, τ^2= 0.012. The heterogeneity was substantially reduced compared with the MA of the composite visual tests. BPD patients' ToM deficit in visual tasks without RMET was more robust compared to that in RMET (Q_{bet}=6.7, P=0.01, n=8+6).

In individual task analyses, there was no significant deficit in BPD patients' accuracy in RMET (d=0.12, n=8; see above by mental state decoding); however, there were significant impairments of BPD patients in performing the FPT (d=-1.07, P<0.001, n=5), the ToM cartoons (d=-0.59, P<0.001, n=4), as well as the MASC (d=-0.46, P<0.01, n=4) (Table 8). When comparing ToM impairments in the individual task types pairwise with post-hoc Holm-modified Tukey procedure, we detected a significant difference only between the RMET and FPT (d=1.19, Z=4.12, P<0.001).

3.4.5. Meta-regression analyses

In the meta-regression analyses, there was no moderating effect of age, education, and gender (the ratio of females in the BPD group compared to that in the HC group). However, the summed rate of panic disorder, generalized anxiety disorder, and phobias (n=9) had a significant positive effect on BPD patients' overall ToM performance compared to HC (Z=2.11, P=0.035; the proportion of total between-study variance explained by model: R^2=0.32). Also, the summed prevalence rate of panic, generalized anxiety disorders, and any phobias (n=9) had a significant positive effect on BPD patients' affective ToM performance compared to HC (Z=2.06, P=0.04; the proportion of total between-study variance explained by model: R^2=0.34). There was no other significant relationship between any other comorbidity variables and ToM performances.

3.5. Discussion

3.5.1. Main results

The main finding of our MA is that BPD patients are significantly impaired in their overall ToM capacities compared to HC; however, the effect size was relatively small.

Another important finding of the present study is that BPD patients' mental state decoding capacities (measured by RMET) do not significantly differ from those of HCs. In contrast, BPD patients' mental state reasoning was found to be significantly worse compared to HC subjects. Q_{bet}-test revealed that BPD patients' mental state reasoning ability was significantly worse than their mental state decoding ability.

The RMET contains subtle emotional information that taps a wider range of mental states beyond the basic emotions. Requiring no reasoning about cognitive and affective mental contents, as well as no contextual processing, the RMET is regarded as an appropriate task to measure the initial, decoding (or discriminating) ToM processes, predominantly the decoding of subtle facial affective cues. A recent MA collapsing RMET performances across 5 studies reported significantly impaired RMET accuracy in neutral valences in BPD patients, while co-occurring MDD enhanced their performance in general, and on positive valence scores (Richman and Unoka, 2015). In our more extended MA (n=8), we could not replicate this finding: we found no moderating effect of the current major depressive episode (MDE), and only BDP patients' enhanced accuracy in negative valences could be detected (significant at the trend level).

The latter result is in accord with theories about BPD patients' sensitivity to negative stimuli, which seems to be characteristic of BPD independently of coexisting depression. BPD patients' relative sensitivity for other peoples' negative mental states is in agreement with the amygdalar hyper-reactivity and altered functional connectivity observed in functional neuroimaging studies during RMET and facial emotion recognition tasks (Donegan et al., 2003; Minzenberg et al., 2007; Cullen et al., 2011; Frick et al., 2012). Our results also fit well with the theory of Fonagy and Bateman (2008): BPD patients who grow up in a non-reflecting, non-validating, and often abusing family environment develop an increased emotional vigilance to social stimuli, especially to those with negative emotional content. Nevertheless, BPD patients' ToM abilities are just partially developed, since their reflective awareness is low, and their mental state reasoning abilities are significantly impaired.

However, findings with RMET in BPD were rather inconsistent, which was basically

due to three studies: in each, BPD patients overperformed normal controls. The first study by Frick et al. (2012) comprised only non-medicated females with a relatively low BDI score and less severe comorbid psychopathology in the BPD group. The second study by Fetruck et al. (2009) recruited patients from the acute setting with more severe comorbid psychopathologies including numerous suicide attempters. Here, the percentage of males was significantly higher in the HC than in the BPD group. In the third study by Zabihzadeh et al., (2017), 50% of the BPD patients suffered from clinically relevant MDD, and the patients were recruited mainly from acute settings. In this study, the proportion of males was exceptionally high but there were no between-group differences in gender ratio. In sum, neither the setting where the patients were recruited, nor the severity of the comorbid psychiatric pathologies, nor the gender ratio of the groups could ultimately explain the relatively good performance of the BPD groups in these studies. Thus, our present MA proposes that the between-study variability of the RMET results seems to be multifactorial, as no consistent reason for the heterogeneous RMET performances could be found.

Furthermore, we detected BPD patients' impaired cognitive ToM capacities, while their affective ToM abilities were relatively preserved. Based on that, one can presume that BPD patients' interpersonal difficulties are mainly due to their deficits in cognitive ToM. This finding can be in agreement with the theoretical framework of the dissociability of affective and cognitive mentalization (Bateman and Fonagy, 2016). Bateman and Fonagy indicate that different forms of psychopathological states are related to the inhibition, deactivation, or simply dysfunction of either the cognitive or the affective or both aspects of mentalization. Patients with BPD are typically overwhelmed by automatic and affect-driven mentalizing, but they have difficulties in integrating affective experiences with reflective and cognitive knowledge. Nevertheless, the latter clinical observation can be in line with our meta-analysis of affective ToM subgroups. After reanalyzing our affective ToM data without RMET, we found that BPD patients significantly underperformed HC in affective ToM tasks. Accordingly, we can suppose, that BPD patients' relatively intact affective ToM capacities are attributable to their affective decoding and discriminating capacities measured by RMET.

However, when we compared BPD patients' cognitive and overall affective ToM deficits with Q_{bet}-test, BPD patients' cognitive ToM deficits were not significantly worse than that of their overall affective ToM. Notably, we got a similar result when we compared affective ToM without RMET with cognitive ToM. Thus, we should carefully interpret our MA results with affective and cognitive ToM, especially because the number of studies that

published affective and cognitive ToM scores separately was low. Future research with simultaneous affective and cognitive ToM measures is needed to understand the exact nature of dissociation of affective and cognitive ToM in BPD.

3.5.2. The effect of comorbidities on theory of mind in BPD

The summed rate of DSM-5 anxiety disorders (primarily panic disorder, agoraphobia, specific phobia, social anxiety disorder, and generalized anxiety disorder) has been proofed to have a positive effect on BPD patients' overall ToM performance and their affective ToM abilities. Among the anxiety disorders, social anxiety disorder presents most typically social dysfunctions and interpersonal difficulties. In a handful of studies that have been published so far, patients with social anxiety disorder were found to have various deficits of ToM decoding and reasoning (Hezel and McNally, 2014; Buhlmann et al., 2015; Washburn et al., 2016). Interestingly, no significant relationship could be detected between comorbid social anxiety disorder and ToM in our MA. Similarly to the summed prevalence of anxiety disorders, only study-level data (from 9 studies) were available, with no measures of current, individual symptom severity.

A very recent study reported that patients with generalized anxiety disorder displayed more accurate mental state reasoning capacities compared to HC, especially when they suffered from increased worry (Zainal and Newman, 2018). Although there are no data in the literature about ToM capacities in panic disorder, agoraphobia, or simple phobia, one can assume that worry, concern, and continuous anticipatory anxiety can induce a state of hypervigilance, where people have an increased need for contact with and support from others. These factors might enhance BPD patients' interpersonal sensitivity and ToM capacities if they have comorbid anxiety disorders. Nevertheless, further research is needed to specify the effect of comorbid anxiety disorders in BPD on ToM capacities.

In contrast to previous findings in BPD patients with comorbid depression, our meta-regression analyses did not reveal any effect of comorbid MDD, neither on overall ToM performance nor on any other ToM dimensions or components. There is some evidence for enhanced ToM abilities in non-clinical samples with dysphoria (measured by Beck Depression Inventory; dysphoria scored > 12) (Harkness et al., 2005, 2010). Nonetheless, no studies included in our MA measured subthreshold or subclinical depression.

3.5.3. The effect of task type

Verbal and multimodal task types revealed significantly impaired ToM in BPD. For visual tasks, however, there was no significant difference between BPD patients' and HCs' ToM performance. Presumably, the latter result was due to the effect of RMET. When visual tasks were reanalyzed without RMET, BPD patients were found to be significantly impaired in visual tasks. In addition, BPD patients showed significantly fewer impairments in RMET than in other visual tasks (i.e., cartoons+ MET).

Meta-analyses results of individual task types were more consistent than those of subgroups by the predominant modality of stimuli, and revealed, that except RMET, all other test types detected ToM deficits in BPD patients. The largest effect size was found with the FPT, while MA for overall verbal tasks, cartoons with different content, movies, and MASC yielded medium effect sizes.

Accordingly, the FPT seems to be the most demanding ToM task for BPD patients. FPT (Stone et al., 1998) comprises stories describing complex social situations, where a character commits a conversational failure by saying something (s)he should not say or saying something awkward. The FPT encompasses high contextual demands and requires implicit integration of cognitive inferences about mental states. Moreover, the FPT is purely verbal, thus patients with BPD cannot rely on their enhanced sensitivity to non-verbal emotional stimuli while performing the FPT.

Several types of ToM cartoons were used in studies involved in our MA, in which participants needed to understand social situations presented in the cartoons and represent the characters' minds, to find chronological order, or understand irony, humor, and false beliefs. BPD patients were found to underperform HCs in more complex cartoon tasks (e.g., CAMS; Dimaggio and Brüne, 2010; or JAT; Langdon et al. 2010) where not only cartoon sequencing but a subsequent answering of questions about the cartoon characters' mental states, or integration of multiple perspectives to decipher humor were also required (Brüne et al, 2016; Petersen et al., 2016).

In sum, all tasks with a higher level of complexity detected ToM impairments in BPD patients. In BPD research, several authors emphasize the importance of ToM tasks with high ecological validity (Minzenberg et al., 2006, Dyck et al, 2009; Roepke et. al, 2013; Baez et al., 2015). Displaying real-life situations, the Multifaceted Empathy Test (MET), as well as the video-based ToM tasks (MASC, TASIT), are regarded as ecologically valid. Especially, video-based tasks entail the integration of several cues from faces, gestures, and prosody, along with those of the social context. Of note, MASC is unique, because it measures several forms of mentalizing errors (i.e., hypomentalizing, hypermentalizing). So far, only 4 studies

have used MASC in ToM research in adults with BPD. Further research is recommended using MASC in BPD patients to evaluate how sensitively MASC detects specific hypermentalizing tendencies in BPD.

3.5.4. Limitations

Unexpectedly, meta-regression analyses revealed no moderating effect of the comorbid MDE and PTSD. Since no sufficient data on the individual symptom severity of depression were available, we conducted the analyses with study-level data. Hence, it was not possible to disentangle or weigh the effect of mild and severe comorbid depression on ToM. Neither, we detected the moderating effect of comorbid PTSD. Similarly to MDE, only the percentage of comorbid PTSD in the samples, but no other clinical variables (such as symptom severity, chronicity or acuteness, co-occurrence with dissociative symptoms, time and nature of the traumatic event, etc.) were available. There is increasing evidence that adverse childhood life events and insecure attachment play a crucial role in BPD patients' mentalizing deficits (Fonagy et al., 2003). Unfortunately, only a few studies included in the MA quantified the quality of parental care or the severity of adverse childhood life events in BPD patients (e.g., Ghiassi et al., 2010; Brüne et al., 2016; Petersen et al., 2016).

The missing data on medications made it impossible to analyze and reveal any medication effect on ToM impairments. Furthermore, only one study in our MA assessed BPD patients' neurocognitive functions, and their correlation with ToM performances (Baez et al., 2015), therefore the impact of neurocognitive functions on ToM could not be evaluated.

Only 4 studies measured mental state decoding and reasoning in the same sample simultaneously, therefore it was not possible to compare data only from studies with simultaneous measures. So we performed the Q_{bet}-test with all studies for mental state decoding (n=8), and reasoning (n=13). Although samples partially overlap, we present this result, because the 95% *CI* of effect sizes showed no overlap. Nevertheless, this is an obvious limitation and requires revision in the future, when more simultaneous measures are available.

4. Examining the relationship between executive functions and mentalizing abilities of patients with borderline personality disorder

4.1. Introduction

Borderline personality disorder (BPD) is a psychiatric condition characterized by three symptom clusters including affective dysregulation, impulsivity, and disturbed relatedness (Sanislow et al., 2002). According to the mentalization-based model of BPD (Sharp and Kalpakci, 2015; Fonagy and Luyten, 2016), these features of BPD can be viewed as a consequence of impairments in the capacity to mentalize, i.e., to understand behavior in terms of underlying mental states. In this theory, mentalization is defined as a multidimensional construct involving several dimensions and abilities. One of these dimensions relates to the objects of mentalizing: it can be directed either toward the mental states of the self or toward the mental states of others.

Impairment of self-oriented mentalizing can be manifested as low levels of emotional self-awareness or alexithymia (Choi-Kain and Gunderson, 2008). Alexithymia is a clinical condition characterized by an inability to identify and describe one's own affective experiences (Taylor et al., 1997). Studies have found that borderline patients are more alexithymic than healthy controls (for a meta-analysis, see Derks et al., 2017) and reported relationships between BPD individuals' alexithymic traits and the severity of their symptoms (e.g., Gaher et al., 2013; McMain et al., 2013). However, to date, no attention has been paid to the potential neurocognitive underpinnings of alexithymia in BPD.

Other-oriented mentalizing can be operationalized as theory of mind (ToM) (Choi-Kain and Gunderson, 2008), a social-cognitive function by which we can attribute mental states, such as beliefs, intentions, and emotions, to others (Baron-Cohen et al., 1985). ToM is a multi-component construct and consists of several subprocesses (Tager-Flusberg and Sullivan, 2000; Sabbagh, 2004). Mental state decoding is the social-perceptual aspect of ToM, which involves the ability to detect and discriminate others' mental states based on their observable social behavior. Mental state reasoning implies the social-cognitive subcomponent, involving causal inferences and predictions about others' mental states based on additional information sources including context and general social knowledge.

Findings on ToM performance in BPD indicate that the decoding and reasoning subprocesses of ToM may be unequally affected by the disorder. Several studies have found that BPD patients exhibited intact or even enhanced ability to decode others' mental states

based on facial expressions (Fertuck et al., 2009; Frick et al., 2012; Zabihzadeh et al., 2017). By contrast, other studies have shown that borderline patients perform worse than healthy controls on ToM reasoning tasks (Harari et al., 2010; Preißler et al., 2010; Brüne et al., 2016), but the severity of their deficit is task-dependent (Petersen et al., 2016). It has been suggested that BPD patients' ToM impairment becomes apparent in more complex tasks that require contextual processing and the integration of multiple mental state perspectives (Baez et al., 2015; Brüne et al., 2016; Petersen et al., 2016). This raises the possibility that the difficulties of BPD patients in ToM reasoning are not due to deficits in their basic ToM abilities but rather to deficits in neurocognitive skills, mainly in executive functioning.

Executive functioning (EF) refers to capabilities that enable flexible and goal-directed responses in novel or complex situations. Through the higher-order monitoring and regulation of cognitive subprocesses, EF plays an important role in the operation of many cognitive functions (Chan et al., 2008). The role of EF in mentalizing abilities is a widely investigated topic in both clinical and non-clinical samples. Regarding emotional awareness, it has been hypothesized that the cognitive systems which are responsible for the higher-level elaboration of emotional experiences are not specialized for emotional processing but rather implement domain-general executive functions (LeDoux, 2000; Lane and Garfield, 2005). This notion implies that executive dysfunction may cause disturbances in emotional self-awareness. Supporting this idea, several studies have found a relationship between poor performance on EF tasks and alexithymic symptoms (e.g., Henry et al., 2006; Santorelli and Ready, 2015).

Concerning the EF-ToM relationship, it has been suggested that these two abilities are implemented by two separate but interacting cognitive systems (Stone and Gerrans, 2006; Aboulafia-Brakha et al., 2011; Wade et al., 2018). According to this view, there are cognitive mechanisms specifically involved in the representation of the mental states of others, but domain-general executive processes are required to efficiently manage and properly apply those representations in complex circumstances. In line with this assumption, many behavioral studies have demonstrated that performance on EF tests shows association with ToM performance, mainly in the case of those complex ToM tasks that have high cognitive load and contextual demands (Aboulafia-Brakha et al., 2011; Ahmed and Miller, 2011). These results suggest that EF is more strongly related to the reasoning aspect of ToM than to the decoding component.

There is a lack of research on the relationship between mentalizing abilities and EF in BPD. This limitation is particularly striking in light of several studies that have demonstrated

structural and functional abnormalities in frontal executive brain areas and impaired behavioral performance on executive tasks in borderline patients (for reviews, see Krause-Utz et al., 2014; McClure et al., 2016). Although executive dysfunctions in BPD were mainly investigated and discussed in relation to symptoms of affective and behavioral dysregulation (e.g., Fertuck et al., 2006; LeGris and Van Reekum, 2006), these deficits may play an important role in BPD patients' mentalizing impairments, as it is the case in many psychiatric and neurological disorders.

4.2. Objectives

The present study addressed two main objectives. The first aim was to parallelly analyze the mentalizing and executive neuropsychological profiles of patients with BPD by comparing their performance to matched healthy individuals on tasks assessing different subdomains of mentalization and executive control. We examined both other- and self-oriented mentalizing, which we operationalized following literature guidelines (Choi-Kain and Gunderson, 2008; Bateman and Fonagy, 2016) as ToM and emotional self-awareness/alexithymia, respectively. Based on earlier studies suggesting that BPD patients may have intact mental state decoding capacity but deficits in mental state reasoning (Németh et al., 2018), we decided to investigate these two aspects of ToM separately. Regarding EF assessment, we followed current notions about the fractionation of EF into different subcomponents (Miyake et al., 2000; Fisk and Sharp, 2004), and used well-validated neuropsychological measures of mental set-shifting, working memory updating, prepotent response inhibition, and long-term memory access to compare the executive abilities of patients and controls. Our second aim was to perform multivariate analyses to determine the relative importance of BPD diagnosis and global executive functioning in predicting alexithymia, as well as ToM performance while considering the potential confounding effects of psychiatric symptom severity and general intelligence.

4.3. Methods

4.3.1. Participants

Eighteen patients with BPD (17 females and 1 male) were recruited from the Affective Disorder Unite of the Department of Psychiatry and Psychotherapy, University of Pécs. All

patients were between 18 and 50 years old and fulfilled the DSM-5 diagnostic criteria for BPD (APA, 2013). The diagnoses were established by a trained psychiatrist using the Structured Clinical Interview for DSM-5, Clinical Version (SCID-5-CV; First et al., 2016), and the Structured Clinical Interview for DSM-5, Personality Disorders (SCID-5-PD; First et al., 2018). Exclusion criteria for the patient group were any other personality disorder, psychotic disorders, bipolar disorder, post-traumatic stress disorder, current substance use disorder, a history of head injury, neurological diseases, and intellectual disability. Treatment with psychotropic medication or psychotherapy was not exclusion criteria once the diagnosis had been established. At the time of the investigations, 17 of the 18 patients were on psychotropic medication.

The control group consisted of 18 healthy subjects (17 females and 1 male) recruited through online advertisements. Healthy controls (HC) were matched pairwise to the patients for gender, age (± 4 years), years of education (± 2 years), and intelligence level (± 5 points). Exclusion criteria for controls included any mental disorder, a history of substance abuse, a history of neurological disorders and head injury with loss of consciousness for more than 30 minutes, an IQ < 85, and any learning difficulties. In addition, the Hungarian version of Symptom Check List-90-Revised (Unoka et al., 2004) was applied to rule out current psychiatric symptomatology in healthy individuals. None of the healthy individuals took psychotropic medication. The demographic and clinical data are presented in Table 9.

All subjects gave written informed consent and the study was approved by the Research Ethics Committee of the Faculty of Humanities, University of Pécs (Ethical Approval No.: 2015/1).

4.3.2. Instruments

4.3.2.1. Symptom assessment

The severity of psychiatric symptoms was assessed with the Symptom Check List-90-Revised (SCL-90-R; Derogatis, 1977). The SCL-90-R is a 90 item self-report questionnaire designed to measure psychological distress in terms of nine primary symptom dimensions: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. The Hungarian version of the SCL-90-R showed good construct validity and acceptable internal consistency (Unoka et al., 2004). In the present study, we used the Global Severity Index (GSI; the mean score of all 90 items)

of the instrument.

4.3.2.2. Estimation of intelligence

The overall level of intelligence (IQ) was estimated with a four-subtest version of the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Kaufman et al., 1991). This short form of WAIS-R is composed of Arithmetic, Similarities, Picture Completion, and Digit Symbol subtests, and it has been shown that it provides a precise estimation of the full-scale WAIS-R IQ with a validity coefficient of 0.95 (Kaufman et al., 1991).

4.3.2.3. Executive function tasks

Four subdomains of executive functioning were measured: (1) mental set-shifting (with Wisconsin Card Sorting Test [WCST]; Berg, 1948); (2) working memory updating (with Listening Span Task [LST]; Daneman and Blennerhassett, 1984); (3) prepotent response inhibition (with Eriksen Flanker Task [FT]; Eriksen and Schultz, 1979), and (4) long-term memory access (with Letter Fluency Task [LFT]; see Strauss et al., 2006). The WCST and the FT were computerized tasks taken from the Psychology Experiment Building Language test battery (Mueller and Piper, 2014). In the cases of the LST and the LFT, validated Hungarian adaptations were used (Janacsek et al., 2009; Tánczos et al., 2014). The EF variables of interest were the number of perseverative errors on the WCST, the number of words remembered in the LST, the interference time on the FT, and the number of words generated in the LFT. To get a global measure of executive functioning, we calculated an average *z*-score from these four EF variables, which was converted into a *t*-score (= composite EF score).

4.3.2.4. Alexithymia questionnaire

The level of emotional self-awareness/alexithymia was surveyed using the total scores of the 20-item self-report Toronto Alexithymia Scale (TAS-20; Bagby et al., 1994). The TAS-20 assesses three facets of alexithymia: (1) difficulty identifying feelings; (2) difficulty describing feelings; and (3) externally oriented thinking. The Hungarian validation of the instrument reproduced the original structure with three subscales, and yielded similar internal consistencies (Cserjési et al., 2007).

4.3.2.5. Theory of mind tasks

ToM capacities were examined with two standard ToM tasks. To measure ToM decoding ability, we used the Reading the Mind in the Eyes Test (RMET; Baron-Cohen et al., 2001; Hungarian adaptation: Ivády et al., 2007). This task is composed of 36 black-and-white photographs depicting the eye region of faces expressing complex emotions or intentions. For each photograph, four mental state words were displayed, and the participants' task was to decide which one best described what the person in the picture was feeling or thinking. As the RMET requires recognition of others' mental states based on static and socially decontextualized perceptual stimuli, it does not necessitate contextual processing and complex inferences about mental states. Thus, the RMET is regarded as a prototypical task to measure the social-perceptual, decoding aspect of ToM (Sabbagh et al., 2004; Bora et al., 2006; Richman and Unoka, 2015).

The reasoning component of ToM was examined with the Faux Pas Test (FPT; Stone et al., 1998) in Hungarian translation, which had been successfully used in previous studies with healthy and clinical samples (Gál et al., 2011, 2014). This task consists of 20 short stories about different interpersonal situations that may or may not contain a social faux pas. After each story, participants were asked whether any of the story characters said something awkward. If participants said yes, further questions were raised regarding the characters' cognitive and affective mental states. As a story-based verbal task, the FPT does not involve perceptual processing and requires causal inferences about the characters' mental states on the basis of information provided by the contextual scenes and general social knowledge. Based on these features, the FPT is regarded as an appropriate task to investigate the social-cognitive, reasoning aspect of ToM (Wang et al., 2008; Thoma et al., 2013; Faiśca et al., 2016).

4.3.3. Statistical analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS), version 21.0. Between-group differences in demographic, clinical, neuropsychological, alexithymia, and ToM variables were analyzed using independent-samples *t*-tests. Before conducting group comparisons, the normality of data was checked with normal probability plots and the Shapiro-Wilk test. The

homogeneity of variances was assessed with Levene's statistics. If the homogeneity assumption was violated, Welch's *t*-test was used for group comparisons. For EF and mentalizing measures, we calculated Cohen's *d* effect sizes. After the group comparisons, multiple linear regression analyses were run in the whole sample to explore the significant predictors of alexithymia and ToM. In the regression models, the total scores of TAS-20, RMET, and FPT were separately taken as dependent variables. BPD diagnosis (coded as a dummy variable: 0 = absence of the diagnosis, 1 = presence of the diagnosis), SCL-90-R Global Severity Index, estimated IQ, as well as the composite EF score, were used as predictors in all models. These predictors were included in the multiple regression models in one step using the Enter method. Prior to the regression analyses, multicollinearity diagnostics were done by calculating the variance inflation factor (VIF). All VIF values were well below the general cut-off of 10, ranging from 1.44 to 5.19, with a mean value of 3.09. Normality of residuals was confirmed using normal probability plots and the Shapiro-Wilk test. To estimate the effect sizes of the predictors, Cohen's f^2-values were calculated. In all analyses, *P*-values (two-tailed) ≤ 0.05 were considered statistically significant.

4.4. Results

4.4.1. Between-group comparisons: demographic and clinical data

The demographic and clinical features of BPD and HC groups are shown in Table 9. The groups were matched in terms of gender, age, education level, and estimated IQ. On the SCL-90-R questionnaire, the BPD group had significantly higher depression, anxiety, and global severity scores than the controls (all $P<0.001$).

4.4.2. Between-group comparisons: executive functioning

Group means and results of between-group comparisons for EF and mentalizing performances are presented in Table 10. There were no significant between-group differences in any EF domains. We found a medium effect size for the composite EF (Cohen's d=-0.54) and inhibition scores (Cohen's d=0.60), with a trend level significance of between-group difference for the latter one (P=0.081).

4.4.3. Between-group comparisons: mentalizing abilities

The BPD group had a significantly higher alexithymia score on the TAS-20 relative to the HC group (P<0.001, Cohen's d=1.31). In our sample, ToM decoding (RMET) performances in the two groups did not significantly differ. However, the BDP group showed a significant impairment in ToM reasoning (P=0.026, Cohen's d=-0.78), as demonstrated by their lower mental state inference score on the FPT.

TABLE 9. Demographic and clinical characteristics of the study samples.

	BPD (*n*=18)	**HC (*n*=18)**	***t*-value**	***P*-value**
Demographics				
Gender ratio (female/male)	17/1	17/1		
Age in years (mean ± SD)	34.72 ± 8.02	34.11 ± 9.39	0.210	0.835
Education level in years (mean ± SD)	12.78 ± 3.30	12.89 ± 2.78	-0.240	0.812
IQ estimate (mean ± SD)	109.79 ± 8.22	112.99 ± 8.60	-1.139	0.262
Psychiatric symptom severity				
SCL-90-R depression (mean ± SD)	2.68 ± 0.81	0.47 ± 0.41	10.345	**< 0.001**
SCL-90-R anxiety (mean ± SD)	2.40 ± 0.78	0.38 ± 0.37	9.961	**< 0.001**
SCL-90-R GSI (mean ± SD)	2.06 ± 0.66	0.40 ± 0.28	9.769	**< 0.001**
	n	***%***		
Current comorbid disorders				
Depressive disorders	10	55.5		
Anxiety disorders	6	33.3		
Substance use disorders	5	27.7		
Eating disorders	1	5.5		
Medications				
Antidepressants	11	61.1		
Benzodiazepines	13	72.2		
Mood stabilizers	9	50		
Antipsychotics	16	88.8		

Statistically significant results are presented in bold. BPD, borderline personality disorder; HC, healthy controls; IQ, intelligence quotient; SCL-90-R, Symptom Check List-90-Revised; GSI, Global Severity Index; SD, standard deviation.

TABLE 10. **Executive functions and mentalizing abilities in patients with borderline personality disorder (BPD) and healthy controls (HC).**

	BPD (*n*=18)		HC (*n*=18)		*t*-value	*P*-value	Cohen's *d*
	Mean	SD	Mean	SD			
Executive functions							
Shifting (WCST perseverative errors)[a]	10.61	5.20	8.78	4.91	1.088	0.284	0.36
Updating (LST working memory span)	3.37	0.68	3.65	0.89	-1.046	0.303	-0.35
Inhibition (FT interference time)[a]	43.85	23.74	29.17	25.17	1.800	0.081	0.60
Access (LFT total words)	50.39	15.21	51.78	16.44	-0.263	0.794	-0.09
Composite executive function score	46.62	6.76	50.00	5.65	-1.629	0.113	-0.54
Mentalizing							
Alexithymia (TAS-20 total score)[a]	59.00	12.78	43.67	10.48	3.936	**< 0.001**	**1.31**
ToM decoding (RMET total score)	24.67	4.17	25.56	2.77	-0.753	0.457	-0.25
ToM reasoning (FPT total score)	27.78	5.94	31.89	4.55	-2.332	**0.026**	**-0.78**

Group means and between-group comparisons. Statistically significant results are presented in bold. [a] Higher scores indicate worse functioning. Cohen's *d* values of 0.2, 0.5, and 0.8 represent small, medium, and large effect sizes, respectively. BPD, borderline personality disorder; HC, healthy controls; WCST, Wisconsin Card Sorting Test; LST, Listening Span Task; FT, Flanker Task; LFT, Letter Fluency Task; TAS-20, Toronto Alexithymia Scale-20 items; RMET, Reading the Mind in the Eyes Test; FPT; Faux Pas Test; SD, standard deviation.

4.4.4. Regression analyses in the whole sample: alexithymia

The multiple regression model predicting alexithymia was significant, explaining 56.9% of the variance in the TAS-20 scores. The diagnosis of BPD, the estimated IQ, and the composite EF score were non-significant predictors with small-to-medium effect sizes. General psychiatric symptom severity was the only significant predictor in the model (P=0.002, Cohen's f^2=0.36) (Table 11).

4.4.5. Regression analyses in the whole sample: mental state decoding

The multiple regression model predicting ToM decoding accuracy was significant, accounting for 29.2% of the variance in the RMET scores. In this model, BPD diagnosis predicted significantly better performance on the RMET (P=0.05, Cohen's f^2=0.14). However, greater psychiatric symptom severity was related to significantly worse performance (P=0.021; Cohen's f^2=-0.19). The cognitive variables were non-significant predictors with small effects (Table 11).

4.4.6. Regression analyses in the whole sample: mental state reasoning

The multiple regression model predicting ToM reasoning ability was significant, with 49.8% of the variance in the FPT scores accounted for by the predictors. BPD diagnosis was a significant negative predictor of FPT performance (P=0.032, Cohen's f^2=-0.16). Higher estimated IQ and composite EF scores predicted significantly better performance on the FPT (P=0.015, Cohen's f^2=0.21, and P=0.007, f^2=0.27, respectively). Only the general symptom severity was a non-significant predictor in this model (Table 11).

TABLE 11. Multiple regression models for mentalizing abilities.

Variables	*B*	Std. Error	Beta	*t*-value	*P*-value	Cohen's f^2
Alexithymia[a]						
Constant	73.288	26.942		2.720	0.011	
BPD diagnosis	-5.479	6.694	-0.200	-0.818	0.419	-0.02
Symptom severity	12.797	3.805	0.904	3.363	**0.002**	**0.36**
IQ estimate	-0.308	0.233	-0.187	-1.322	0.196	-0.06
Executive functioning	4.271	3.098	0.196	1.379	0.178	0.06
Theory of Mind decoding[b]						
Constant	25.170	8.749		2.877	0.007	
BPD diagnosis	4.440	2.174	0.640	2.043	**0.050**	**0.14**
Symptom severity	-3.015	1.236	-0.841	-2.440	**0.021**	**-0.19**
IQ estimate	0.014	0.076	0.034	0.187	0.853	0.00
Executive functioning	0.805	1.006	0.146	0.800	0.430	0.02
Theory of Mind reasoning[c]						
Constant	1.224	11.743		0.104	0.918	
BPD diagnosis	-6.559	2.918	-0.592	-2.248	**0.032**	**-0.16**
Symptom severity	2.767	1.658	0.484	1.669	0.105	0.09
IQ estimate	0.262	0.101	0.394	2.577	**0.015**	**0.21**
Executive functioning	3.895	1.350	0.442	2.885	**0.007**	**0.27**

Predictors of mentalizing abilities in the whole sample (n = 36). Statistically significant results are presented in bold. [a] $F_{(4,31)}$=10.24, P<0.001; [b] $F_{(4,31)}$=3.19, P<0.026; [c] $F_{(4,31)}$=7.70, P<0.001. Cohen's f^2-values of 0.02, 0.15, and 0.35 represent small, medium and large effect sizes, respectively. BPD, borderline personality disorder; IQ, intelligence quotient.

4.5. Discussion

This is the first study to examine the relationship between EF, alexithymia, and ToM in BPD, while simultaneously considering the confounding effects of psychiatric symptom severity and general IQ. Our results strengthen the notion that BPD patients' mentalizing subdomains are dissociated: their emotional self-awareness and ToM reasoning was impaired, while their ToM decoding was comparable with those of healthy controls. In a series of multiple regression models, we tested the relative predictive value of EF, IQ, the comorbid clinical symptoms, and the diagnosis of BPD on mentalizing capacities. Comorbid psychiatric symptoms had significantly negative relative importance while predicting self-awareness/alexithymia and ToM decoding. The diagnosis of BPD has been proved to be a significant negative predictor of ToM reasoning but a positive predictor of decoding. EF and IQ positively influenced BPD patients' ToM reasoning.

4.5.1. The executive and mentalizing profile of BPD

For assessing EF, we adopted theories about the fractionation of EF into different subcomponents (Miyake et al., 2000; Fisk and Sharp, 2004). Although our findings regarding EF abilities were not significant, we found worse global EF performance in BPD subjects relative to healthy controls with a medium effect size. The obtained effect size (Cohen's *d*=-0.54) was exactly the same that was reported for EF in a recent meta-analysis on neuropsychological functioning in BPD (Unoka and Richman, 2016). The lack of significance in the present study is presumably due to the low statistical power resulting from our small sample size. When analyzing individual EF domains, we found that borderline patients demonstrated poorer abilities than healthy individuals in three areas: they showed a medium effect size deficit for the inhibition component and small-to-medium effect size impairments for the shifting and updating components. These results are in concordance with prior studies suggesting that, among EF components, deficits in response inhibition may be of central importance in BPD (Posner et al., 2002; Rentrop et al., 2007; Ruocco et al., 2012; Van Dijk et al., 2014).

With respect to mentalizing assessment, we followed current conceptualizations that define mentalization as a multidimensional construct encompassing several different kinds of capabilities (Choi-Kain and Gunderson, 2008; Bateman and Fonagy, 2016). Applying this theoretical framework, we operationalized self-oriented mentalizing as emotional self-awareness/alexithymia and measured it using the Toronto Alexithymia Scale. We found that BPD patients were significantly impaired relative to controls in their ability to mentalize (recognize and describe) their emotional states, as demonstrated by their significantly higher score on the TAS-20 compared to controls. This finding conforms with most of the previous studies that evaluated alexithymia in BPD using the TAS-20 (Guttman and Laporte, 2002; Loas et al., 2012; New et al., 2012; Lysaker et al., 2017; Berenson et al., 2018; Pluta et al., 2018).

Other-oriented mentalizing was operationalized in our study as ToM. The decoding and reasoning subcomponents of ToM were examined by their prototypical tasks, the Reading the Mind in the Eyes Test, and the Faux Pas Test, respectively. Regarding the decoding aspect, our results imply intact ability in BPD by showing no significant difference between patients' and controls' accuracy on the RMET. This result is in line with the majority of earlier studies (Preißler et al., 2010; Schilling et al., 2012; Baez et al., 2015;

Berenson et al., 2018), but stands in contrast to other investigations that reported better (Fertuck et al., 2009; Frick et al., 2012; Zabihzadeh et al., 2017) or worse RMET performance (Unoka et al., 2015; Anupama et al., 2018; Van Heel et al., 2019) in BPD patients relative to healthy subjects. These discrepancies among studies might be attributed to differences between patient samples with respect to general psychopathology, as discussed later in this paper. In contrast to the decoding aspect, the reasoning aspect of ToM – measured by the FPT – was significantly impaired in our BPD sample compared to HCs. This finding is in accordance with an increasing number of publications (Harari et al., 2010; Baez et al., 2015; Petersen et al., 2016; Zabihzadeh et al., 2017; Pluta et al., 2018) consistently showing that BPD patients display disturbances in mental state reasoning when performing the FPT.

Taken together, our ToM results replicated the results of our recent meta-analysis on BPD patients' ToM abilities (Németh et al., 2018), demonstrating intact decoding performance on the RMET but impaired reasoning performance on the FPT. Moreover, the present findings are consistent with those of earlier studies (Baez et al., 2015; Petersen et al., 2016; Zabihzadeh et al., 2017) that employed these two ToM tasks together on one BPD sample. The findings reported here endorse the results of these studies suggesting that the mentalizing profile of BPD is characterized by a dissociation between the decoding and the reasoning subprocesses of ToM.

4.5.2. Factors influencing mentalizing abilities in BPD

Although in the univariate group comparison we observed a large and significant effect of BPD diagnosis on alexithymia, in the multivariate analysis this effect became small and non-significant. In the multivariate analysis, neither general IQ nor global executive functioning was a significant predictor of alexithymia. However, greater severity of comorbid psychiatric symptoms has been proved to be a relative predictor of a higher TAS-20 score. These findings are in line with prior studies (e.g., Loas et al., 2012; Pluta et al., 2018) demonstrating that borderline individuals are more alexithymic than healthy controls, however, this difference can mainly be explained by their comorbid clinical symptoms, especially by depression and anxiety. Although previous research has demonstrated a relationship between executive functioning and alexithymia in various clinical (Henry et al., 2006; Bogdanova et al., 2010; Bogdanova and Cronin-Golomb, 2013; Smirni et al., 2018) and non-clinical samples (Zhu et al., 2006; Paradiso et al., 2008; Koven and Thomas, 2010;

Zhang et al., 2011; Santorelli and Ready, 2015), our results suggest no relationship between these two abilities in BPD. Nevertheless, our study is the first that investigated this relationship in BPD, thus further research with an extended number of cases is needed on this topic.

Remarkably, the multiple regression analysis predicting ToM decoding ability demonstrated opposing effects of BPD diagnosis and the severity of psychiatric symptoms. While BPD diagnosis predicted better, greater severity of coexisting psychiatric symptoms predicted worse performance on the RMET. As mentioned earlier, in the univariate group comparison, there was no difference between BPD and HC participants on this task. These analyses revealed a statistical suppression situation between BPD diagnosis and the severity of general psychiatric symptoms. One possible explanation for these findings is that BPD patients in our sample may have had a better decoding ability than controls, but this improved ability could be worsened by their comorbid symptoms, resulting in a non-significant difference when the effect of symptoms was not statistically controlled for. Previous studies using the RMET in borderline patients yielded inconsistent results, reporting reduced accuracy (e.g., Unoka et al., 2015; Van Heel et al., 2019), enhanced accuracy (e.g., Fertuck et al., 2009; Zabihzadeh et al., 2017), or no significant difference (e.g., Schilling et al., 2012; Baez et al., 2015) compared to healthy controls. Our findings suggest that the inconsistency of prior studies may be at least partly due to the confounding effect of the severity of psychiatric symptoms.

In contrast to the clinical variables, general IQ and global EF were not significant predictors of RMET scores. These results are in accordance with earlier studies that found no relationship between executive abilities and accuracy on the RMET both in clinical and healthy samples (e.g., Ahmed and Stephen Miller, 2011; Torralva et al., 2015).

In the multivariate analysis predicting ToM reasoning ability, we found that BPD diagnosis was independently related to worse reasoning performance on the FPT, while psychiatric symptom severity was not a significant predictor in the model. However, both higher general IQ and better global EF were independently related to higher FPT scores. Contrary to our RMET results, here we found that better EF was related to improved FPT performance. These findings suggest that these two ToM tasks may rely on different cognitive mechanisms. With its static and decontextualized visual stimuli, the RMET does not require contextual processing and complex reasoning processes. In contrast, the FPT is a verbal task that requires causal inferences about mental states based on short stories in real-life social contexts. In this task, adequate mental state attribution depends both on the ability

to extract relevant information from the context, and on the ability to hold in mind and integrate multiple representations of the characters' different viewpoints and mental states. Thus, beyond the core ability to form representations about others' mental states, optimal performance on the FPT also involves linguistic processing and other non-social cognitive skills. Therefore, the FPT imposes an additional cognitive load relative to the RMET, and our results suggest that this additional load uses up mainly executive function resources. These findings are in accordance with those previous studies that examined the EF-ToM relationship using the RMET and the FPT simultaneously on one sample (e.g., Ahmed and Stephen Miller, 2011; Thoma et al., 2013; Baez et al., 2015; Torralva et al., 2015). Our data, together with the results of these studies, support the notion (Tager-Flusberg and Sullivan, 2000) that the higher-order, reasoning aspect of ToM is more closely linked to domain-general cognitive abilities and prefrontal functioning than the lower-order, decoding component.

BPD diagnosis was also independently related to FPT performance in the multiple regression analysis. The negative effect of BPD on FPT performance found in the univariate analysis remained significant in the multivariate model even after adjusting for general IQ, global EF, and psychiatric symptom severity. This suggests that mental state reasoning deficit might be a stable characteristic of the disorder, which is independent both of neurocognitive functioning and the severity of psychopathology. To date, only one study has examined the relationship between EF and ToM in BPD (Baez et al. 2015). Using similar ToM tasks, this research group found deficits both in EF and mental state reasoning in borderline patients. In their multivariate analysis, EF was significantly related to ToM reasoning performance, but BPD diagnosis was not a significant predictor of this ability, suggesting that mental state reasoning deficit is not a core feature of BPD, but is rather a consequence of executive dysfunction. Nevertheless, the small sample size is a major limitation of both studies; the contradictory relationship between EF and ToM in BPD deserves further examination.

4.5.3. Limitations

The main limitation of our study was the low statistical power due to the small sample size. Thus, all of our findings must be treated as preliminary and should be replicated in larger samples. We should very carefully interpret our results especially those with EF. We can assume that our non-significant results in the between-group comparison of EF scores

are largely due to the low number of cases. Moreover, no clinical comparison group was included in the study; therefore, we did not investigate whether the detected mentalizing profile and its confounders are specific for BPD. BPD patients were recruited from the acute clinical setting. We did not examine demographic variables such as marital status and employment and did not follow up on the sample to test how mentalizing abilities, cognitive functions, and clinical symptoms correlated with the demographic variables related to the functional outcome. Due to the high variability of comorbid psychiatric disorders and the psychotropic medications taken by BPD patients, it was not possible to form homogenous subgroups to test the effect of these factors. Although a large proportion of our patients were on psychotropic medication (mainly on low-dose atypical antipsychotics), the impact of psychoactive drugs was not examined here. Finally, we only considered the severity of psychiatric symptoms measured by SCL-90-R; no other clinical questionnaires were applied.

5. Summary and conclusions

5.1. Summary of the findings

The exact underlying mechanisms of neurocognitive factors and social cognition in major depressive disorder (MDD) and borderline personality disorder (BPD) are not yet fully understood. This thesis explores the correlates, such as early life stress (ELS), serum lipids and lipoproteins, clinical symptoms, and comorbid psychiatric disorders, of the neurocognition and social cognition in MDD and BPD. Moreover, little is known about the correlations between neurocognitive performances with social-cognitive abilities, including various aspects of mentalizing skills; therefore, the third study in this thesis focused on these specific questions. Our main research objectives and findings are:

1. In our first investigation, we aimed to examine the potential relationships between depression, ELS, serum lipid profiles, and neurocognitive functioning. Forty-two patients diagnosed with MDD and 20 healthy controls (HC) participated in the study. We assessed the complete lipid profile of the participants, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and two atherogenic indices (TC/HDL-C and LDL-C/HDL-C). The severity of depressive symptoms was measured by the Beck Depression Inventory (BDI; Beck et al., 1961). Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003) was used to assess ELS. Executive functions and attentional processes were assessed by the Wisconsin Card Sorting Test (WCST; Heaton, 1981) and the Conners' Continuous Performance Test-II (CPT; Conners, 2000), respectively.

   We found no significant differences between the entire MDD group and the HCs in the lipid profiles. However, when we divided the MDD patients into two subgroups, those with or without ELS then, we could observe that TG, HDL-C, and TC/HDL-C values were significantly different between the two MDD subgroups, and TG, TC/HDL-C, and LDL-C/HDL-C values were also significantly different between the MDD+ELS patients and controls. Next, the relationships between the severity of depressive symptoms and lipid levels were tested with regression analyses in the entire patient group. Here, we found that depression severity predicted only the level of HDL-C. However, after controlling for the effects of ELS, the severity of depressive symptoms lost its predictive value, while ELS independently predicted the levels of TG, HDL-C, and TC/HDL-C.

When examining the relationships between the different types of ELS and the lipid profile, physical and emotional neglect, as well as physical and emotional abuse showed significant association with some of the lipid parameters, but there were no relationships between sexual abuse and serum lipid concentrations.

Regarding neurocognitive performances, no significant differences were found between the MDD patients and controls, or between the MDD subgroups on the CPT and WCST after adjustments for covariates. Nonetheless, in the regression analyses, depression severity predicted commission errors and detectability on the CPT, as well as conceptual level responses on the WCST. Furthermore, there were significant negative associations between the level of HDL-C and WCST perseverative errors, between LDL-C/HDL-C ratio and WCST total correct responses, and also between the indices LDL-C/HDL-C and TC/HDL-C, and WCST conceptual level responses. However, we could not detect any relationship between the severity of ELS and neurocognitive performance.

The second and third studies of the thesis focused on the mentalizing abilities of patients with borderline personality disorder.

2. The second study performed a meta-analysis of the literature on theory of mind (ToM) in BPD. We assessed the weighted mean effect sizes of ToM performances in BPD compared to healthy controls and investigated the impact of demographic variables and psychiatric comorbidities on the variability of effect sizes across the studies. Seventeen studies involving 585 BPD patients and 501 healthy controls were selected after literature search. Effect sizes for overall ToM, mental state decoding and reasoning, cognitive and affective ToM, and for different task types were calculated.

   We found that BPD patients significantly underperformed healthy controls in overall ToM, mental state reasoning, and cognitive ToM, but had no deficits in mental state decoding. Affective ToM performance was largely task-dependent in BPD. Moreover, we could detect a dissociation between the ToM decoding and reasoning abilities of BPD patients; however, we found no dissociation between the affective and cognitive components of ToM. Comorbid anxiety disorders had a positive moderating effect on overall and affective ToM in BPD; however, the demographic variables had no influence. Among different ToM tasks, the Faux Pas Test was the most sensitive task to detect ToM deficits in BPD.

3. The third study of the thesis was built upon the findings of our meta-analysis. The main objective of this study was to examine the relationship between BPD patients' mentalizing profile and their executive functioning (EF). For this purpose, we compared the mentalizing and executive abilities of BPD patients and healthy subjects and subsequently investigated the relative importance of EF and the diagnosis of BPD in predicting mentalizing abilities (while controlling for general IQ and comorbid symptom severity). Self-oriented mentalizing (operationalized as emotional self-awareness/alexithymia), other-oriented mentalizing (defined as theory of mind), and several EF domains were examined in 18 patients with BPD and 18 matched healthy individuals. The level of emotional self-awareness/alexithymia was surveyed using the Toronto Alexithymia Scale (TAS-20; Bagby et al., 1994), and the decoding and reasoning subprocesses of ToM were assessed by their standard tasks, the Reading the Mind in the Eyes Test (RMET; Baron-Cohen et al., 2001), and Faux Pas Test (FPT; Stone et al., 1998), respectively.

   There were no statistically significant between-group differences in any EF measures. However, BPD patients performed worse than the controls in global EF and the inhibition component of EF with medium effect sizes. BPD patients exhibited significant impairments in emotional self-awareness and mental state reasoning relative to HCs; however, their mental state decoding ability did not differ compared to controls. Multiple regression analyses revealed that comorbid psychiatric symptoms were negative predictors of emotional self-awareness and ToM decoding. Remarkably, the diagnosis of BPD was a positive predictor of ToM decoding but negatively influenced ToM reasoning. Moreover, IQ and EF had no impact on alexithymia and ToM decoding, while better IQ and EF predicted superior ToM reasoning.

5.2. Conclusions and implications for future research and clinical practice

1. Our results with serum lipids and lipoproteins in MDD provide additional evidence that childhood adversity may increase the risk of cardiovascular disease. However, further research is needed to clarify the exact intermediary factors to better understand the physiological mechanisms linking ELS to cardiometabolic disease, including the exploration of differences between and common pathways for specific maltreatments. Importantly, these issues should preferably be investigated in longitudinal studies as the retrospective self-reported measures might be biased. Moreover, future research is

required to delineate the potential adverse effects of serum lipid alterations on neurocognitive functioning in MDD. Finally, the present findings highlight the importance of statistically controlling for the effects of ELS when biological markers of MDD are studied.

Thus, these results are in line with the literature and have important implications for clinical assessment of MDD patients with ELS. Our data emphasize the importance of screening for ELS in the clinical MDD population. Several studies demonstrated that depressed adults who experienced ELS react less well to conventional treatments than those who were not exposed to stressful life events during childhood (reviewed by Targum and Nemeroff, 2019). There is some evidence that MDD with ELS reacts much better to cognitive behavioral therapy (Nemeroff et al., 2003; Niciu et al., 2015) or interpersonal therapy (Zobel et al., 2011) than to pharmacotherapy. Particularly in the case of early emotional abuse and emotional and physical neglect, we should consider psychotherapeutic interventions. Clinicians should be also aware that depressed patients with a history of ELS have elevated risks for somatic complications, such as cardiovascular disease. Therefore, treatment interventions should support early traumatized patients to effectively regulate their negative affective states, and reduce stress, instead of using unhealthy strategies to cope with stressful situations.

2. The results of our meta-analysis provide some important clues for therapy and research on mentalizing abilities in patients with BPD. Although we demonstrated that BPD patients' overall ToM performance significantly differed from that of healthy controls, the effect size of the observed impairment (d=-0.27) was much smaller than that in similar meta-analyses on other psychiatric populations, such as in patients with schizophrenia, bipolar disorder, major depression, or eating disorders (for a review of these meta-analyses, see Cotter et al., 2018). Furthermore, our findings suggest that the mentalizing profile of BPD appears to be disorder-specific as it is characterized by a dissociation between the decoding and the reasoning subprocesses of ToM. This implies that psychotherapeutic interventions aiming to improve mentalizing abilities in BPD may be most effective if they target patients' mental state reasoning abilities and if they support patients to adequately use their preserved decoding abilities. However, as mental state decoding was examined only with the Reading the Mind in the Eyes Test in our meta-analysis, future research should use other decoding tasks to verify our results regarding the dissociation of ToM decoding and reasoning in BPD. Finally, our findings suggest that BPD patients'

ToM impairments become apparent in more complex tasks requiring contextual processing and the integration of multiple mental state perspectives. Based on our meta-analysis findings, the Faux Pas Test seems to be an appropriate tool for evaluating BPD patients' ToM deficits in research and clinical settings.

Our meta-analysis findings may provide a theoretical framework for understanding the so-called "borderline empathy paradox" (Dinsdale and Crespi, 2013). The borderline empathy paradox is based on the clinical observation that individuals with BPD demonstrate enhanced empathy and can sensitively identify other people's mental states; which, however, is in sharp contrast with their highly conflictual interpersonal functioning that is full of misunderstandings. Our results suggest that the core feature of the empathy paradox can be due to BPD patients' difficulties with reasoning about other's mental states despite their above-average abilities to decode mental states based on observable social cues. Accordingly, BPD patients' interpersonal problems are not primarily caused by socio-perceptual deficits but rather by insufficient understanding of the observed behaviors: although they can adequately identify other people's mental states, their ability to make inferences about the triggering events of these mental states and the typical behavioral consequences is impaired.

The dissociation of mental state decoding and reasoning abilities in BPD harmonizes with the attachment-based mentalizing model of BPD established by Fonagy and colleagues (Fonagy and Bateman, 2008; Fonagy and Luyten, 2016). This model emphasizes the role of the emotionally neglectful, intrusive, and often abusive childhood family environment (that does not reflect on and invalidates the subjective experiences and needs) in the evolution of mentalizing abilities typical for BPD. This kind of early environment can stimulate the development of an increased perceptual vigilance to social stimuli; however, at the same time, it can lead to a defensive-type avoidance of thinking about mental states (Fonagy and Bateman, 2008; Fonagy and Luyten, 2016). Hence, a typical profile of mentalizing abilities can emerge by adulthood, where the early, intuitive, stimulus-bound, and less reflective forms of mentalizing dominate over the mature, abstract, reflective, and consciously regulated ones. In absence of the balancing effect of higher-order mentalizing abilities, mentalizing in BPD is typically swift, impulsive, and impression-driven, based on the pure observation of external behavioral signals, and involves predominantly affective states. Thus, BPD patients' mental state attributions are too intense, superficial, and rapid, and it can be difficult to change them by further analysis of the interpersonal situation. In the mentalizing-based treatment (Bateman and

Fonagy, 2010, 2016), the therapist facilitates patients with BPD to use higher-order, reflective, and more controlled forms of mentalizing which are beyond pure observation of social cues and involves both external and internal contextual information. In this way, patients' initial attributions can be reviewed, and a better understanding can be achieved by more accurately mapping the internal drives of others' behavior.

3. In the last study, we revealed some clinical and neurocognitive factors that may influence the mentalizing profile of BPD patients. The results of this study suggest that alexithymia in BPD is explained by the severity of psychiatric symptoms. Furthermore, the diagnosis of BPD is associated with better mental state decoding ability in itself; however, co-occurring clinical symptoms can deteriorate this enhanced ToM decoding ability. Conversely, impairment in mental state reasoning seems to depend on IQ and EF, and can be a core feature of BPD. Hence, this study presents further evidence that there is a dissociation between ToM decoding and reasoning abilities in BPD. However, regarding the low number of cases in this study, we should very carefully interpret the results, and further research is necessary to test our data in a larger clinical sample.

   According to the results of this study, a part of BPD patients' mentalizing abilities appears to be trait-like, while another part of them can be characterized as state-dependent. We found that BPD patients' emotional self-awareness and their ability to decode mental states can vary parallel with the severity of general psychopathology. Thus, based on our limited results, clinicians should carefully monitor BPD patients' psychiatric symptoms and consider that patients' self-awareness and mental state decoding abilities can fluctuate with the severity of their co-occurring symptoms. Conversely, impairment in mental state reasoning seems to be a stable, trait-like feature of BPD which is independent of the clinical symptoms. These findings are consistent with the results of our meta-analysis suggesting that deficits in mental state reasoning are of central importance in BPD and psychotherapeutic interventions may be most effective if they aim to improve BPD patients' ToM reasoning abilities.

   However, in the last study of the thesis, not only BPD diagnosis but also the level of executive functioning was an independent predictor of mental state reasoning capabilities. These results indicate that although mental state reasoning deficit can be present with intact EF abilities in BPD, in a subgroup of patients characterized by executive dysfunctions, we might expect increased ToM reasoning impairment.

   Previous studies have consistently found that executive dysfunctions are associated

with decreased mentalizing abilities in various clinical samples (for reviews, see Pickup, 2008; Aboulafia-Brakha et al., 2011; Wade et al., 2018). The results of these studies suggest that mentalization and EF are implemented by separate but interacting cognitive systems. Specifically, these findings indicate that there are discrete cognitive mechanisms involved in the representation of mental states, but domain-general executive processes are required to modify and successfully apply those mental state representations in complex, real-life circumstances (Wade et al., 2018). Thus, EF does not seem to be sufficient for mentalizing but can facilitate its functioning. In line with this, several studies found in various psychiatric samples that cognitive training programs, which aim to improve EF and other neurocognitive skills, have beneficial effects on patients' mentalizing abilities (Corrigan et al., 1995; Fisher and Happé, 2005; Thibaudeau et al., 2017). These results led to the development of new therapeutic methods (especially for the treatment of schizophrenia) that integrate neurocognitive and social-cognitive remediation techniques to enhance the everyday interpersonal functioning of patients (Eack et al., 2009; Roder et al., 2011; Bechi et al., 2020).

Although neurocognitive deficits in BPD patients can be similar in magnitude to those in patients with schizophrenia (LeGris and van Reekum, 2006; Unoka and Richman, 2016), so far few studies have focused on exploring the feasibility and effectiveness of cognitive remediation in the treatment of BPD. In one such study (Vita et al., 2018), it was found that computer-assisted cognitive training had a positive effect on neurocognition and psychosocial functioning in patients with BPD. As our data and the results of a previous study (Baez et al., 2015) suggest that executive deficits may play a role in mentalizing impairments in BPD, it would be worthwhile to examine in the future whether the effectiveness of mentalization-based psychotherapies could be increased by combining them with executive training programs. Such an integrated treatment approach may be particularly efficient in borderline patients with significant executive dysfunction.

In summary, the research findings presented in this thesis fit well into studies that investigate the social and neurocognitive functions, as well as their various correlates in the clinical populations. In spite of their limitations, our results can be integrated into clinical thinking and can be utilized when assessing and planning therapy for patients with MDD and BPD. Of particular interest are the results that emphasize the role of early life stress in MDD. Also, from a clinical point of view, the findings that harmonize with the mentalization-based framework of BPD and highlight the relevance of co-occurring clinical symptoms, as well as

those that support the importance of cognitive remediation techniques in BPD are worth considering.

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Publications

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Oral and poster presentations related to the thesis

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Supplementary tables

Supplementary Table 1. Results of the one-way ANCOVA comparisons between healthy controls and the entire MDD group in serum lipid and lipoprotein levels.

Total cholesterol	$F_{(1,55)}$=1.021, P=0.317
Triglycerides	$F_{(1,55)}$=0.943, P=0.336
HDL cholesterol	$F_{(1,55)}$=0.546, P=0.463
LDL cholesterol	$F_{(1,55)}$=1.837, P=0.181
LDL-C/HDL-C	$F_{(1,55)}$=2.781, P=0.101
TC/HDL-C	$F_{(1,55)}$=2.298, P=0.135

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

Supplementary Table 2. Neurocognitive test results, and one-way ANOVA results of the comparisons between healthy controls and MDD groups in neurocognitive performances.

	HC (*n*=20)	entire MDD (*n*=42)	MDD Only (*n*=21)	MDD +ELS (*n*=21)	Two-group comparisons	Three-group comparisons
CPT omissions[a]	1.00 (1.00)	2.00 (4.25)	2.00 (4.00)	3.00 (5.00)	Welch's $F_{(1,58.5)}$=7.464, P=0.008	Welch's $F_{(2,36.6)}$=3.780, P=0.032 HC<MDD+ELS, P=0.045
CPT commissions[b]	12.05 (5.17)	14.05 (7.22)	12.10 (5.64)	16.00 (8.19)	$F_{(1,60)}$=1.226, P=0.273	Welch's $F_{(2,38.5)}$=1.943, P=0.157
CPT hit reaction time (msec)[a]	361.80 (40.47)	386.13 (72.14)	376.50 (55.40)	388.30 (80.37)	$F_{(1,60)}$=3.432, P=0.069	$F_{(2,59)}$=2.039, P=0.139
CPT detectability[b]	0.74 (0.36)	0.69 (0.42)	0.73 (0.42)	0.60 (0.47)	$F_{(1,60)}$=0.454, P=0.503	$F_{(2,59)}$=0.769, P=0.468
WCST total correct responses[a]	71.00 (12.25)	70.00 (14.75)	72.00 (18.00)	67.00 (13.50)	$F_{(1,60)}$=0.289, P=0.593	$F_{(2,59)}$=0.681, P=0.510
WCST perseverative errors[a]	7.00 (5.5)	11.00 (21.00)	10.00 (18.50)	17.00 (26.00)	Welch's $F_{(1,50.8)}$=5.463, P=0.023	$F_{(2,59)}$=2.617, P=0.082
WCST non-perseverative errors[a]	8 (7.00)	12.00 (17.25)	15.00 (17.50)	12.00 (16.00)	$F_{(1,60)}$=3.479, P=0.067	$F_{(2,59)}$=1.835, P=0.169
WCST conceptual level responses[b]	66.80 (7.05)	62.33 (13.37)	64.62 (14.60)	60.05 (11.94)	$F_{(1,60)}$=1.960, P=0.167	$F_{(2,59)}$=1.794, P=0.175

[a] Medians and inter-quartile ranges are presented. [b] Means and standard deviations are presented. CPT, Conners' Continuous Performance Test-II; ELS, early life stress; HC, healthy controls; MDD, major depressive disorder; WCST, Wisconsin Card Sorting Test.

Supplementary Table 3. One-way ANCOVA results of the comparisons between healthy controls and MDD groups in neurocognitive performances.

	Two-group comparisons	Three-group comparisons
CPT omissions	$F_{(1,57)}$=1.391, P=0.243	$F_{(2,56)}$=0.897, P=0.414
CPT commissions	$F_{(1,57)}$=0.001, P=0.971	$F_{(2,56)}$=1.329, P=0.273
CPT hit reaction time (msec)	$F_{(1,57)}$=1.522, P=0.222	$F_{(2,56)}$=1.206, P=0.307
CPT detectability	$F_{(1,57)}$=0.102, P=0.750	$F_{(2,56)}$=0.198, P=0.821
WCST total correct responses	$F_{(1,57)}$=1.720, P=0.195	$F_{(2,56)}$=1.495, P=0.233
WCST perseverative errors	$F_{(1,57)}$=0.136, P=0.714	$F_{(2,56)}$=0.207, P=0.813
WCST non-perseverative errors	$F_{(1,57)}$=0.042, P=0.838	$F_{(2,56)}$=0.380, P=0.685
WCST conceptual level responses	$F_{(1,57)}$=1.777, P=0.188	$F_{(2,56)}$=1.487, P=0.235

CPT, Conners' Continuous Performance Test-II; WCST, Wisconsin Card Sorting Test.

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Theory of mind disturbances in borderline personality disorder: A meta-analysis

Nándor Németh[a], Péter Mátrai[b], Péter Hegyi[c,d], Boldizsár Czéh[a,e], László Czopf[f], Alizadeh Hussain[g], Judith Pammer[g], Imre Szabó[h], Margit Solymár[i], Loránt Kiss[j], Petra Hartmann[k], Ágnes Lilla Szilágyi[k], Zoltán Kiss[l], Maria Simon[a,m,*]

[a] Neurobiology of Stress Research Group, Szentágothai János Research Centre, University of Pécs, Pécs, Hungary
[b] Institute of Bioanalysis, University of Pécs, Medical School, Pécs, Hungary
[c] Institute for Translational Medicine and 1st Department of Medicine, University of Pécs, Medical School, Pécs, Hungary
[d] Momentum Translational Gastroenterology Research Group, Hungarian Academy of Sciences University of Szeged, Szeged, Hungary
[e] Department of Laboratory Medicine, University of Pécs, Medical School, Pécs, Hungary
[f] Department of Cardiology, 1st Department of Medicine, University of Pécs, Medical School, Pécs, Hungary
[g] Department of Haematology, 1st Department of Medicine, University of Pécs, Medical School, Pécs, Hungary
[h] Department of Gastroenterology, 1st Department of Medicine, University of Pécs, Medical School, Pécs, Hungary
[i] Institute for Translational Medicine, University of Pécs, Medical School, Pécs, Hungary
[j] Department of Pathophysiology, University of Szeged, Medical School, Szeged, Hungary
[k] Institute of Surgical Research, University of Szeged, Hungary
[l] 1st Department of Paediatrics, Semmelweis University, Budapest, Hungary
[m] Department of Psychiatry and Psychotherapy, University of Pécs, Medical School, Pécs, Hungary

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ABSTRACT

Impairments of theory of mind (ToM) are widely accepted underlying factors of disturbed relatedness in borderline personality disorder (BPD). The aim of this meta-analysis a was to assess the weighted mean effect sizes of ToM performances in BPD compared to healthy controls (HC), and to investigate the effect of demographic variables and comorbidities on the variability of effect sizes across the studies. Seventeen studies involving 585 BPD patients and 501 HC were selected after literature search. Effect sizes for overall ToM, mental state decoding and reasoning, cognitive and affective ToM, and for task types were calculated. BPD patients significantly underperformed HC in overall ToM, mental state reasoning, and cognitive ToM, but had no deficits in mental state decoding. Affective ToM performance was largely task dependent in BPD. Comorbid anxiety disorders had a positive moderating effect on overall and affective ToM in BPD. Our results support the notion that BPD patients' have specific ToM impairments. Further research is necessary to evaluate the role of confounding factors, especially those of clinical comorbidities, neurocognitive functions, and adverse childhood life events. Complex ToM tasks with high contextual demands seem to be the most appropriate tests to assess ToM in patients with BPD.

1. Introduction

Borderline personality disorder (BPD) is a phenomenologically heterogeneous disorder characterized by affective, cognitive, behavioral, and interpersonal (i.e. disturbed relatedness) symptom areas (APA, 2013). It is widely accepted that BPD patients' unstable relational style is of central importance (Gunderson, 2007), and other symptoms, such as impulsivity, self-harm, anger or emotional instability are consequences of, or triggered by the social, interpersonal context (Hepp et al., 2017; Brodsky et al., 2006; Kehrer and Linehan, 1996). Clinical

Abbreviations: ATT, advanced ToM test; BPD, borderline personality disorder; CAMS, cartoon-based assessment of mentalizing skills; EAT, expression attribution test; FER, facial emotional recognition; FBPST, false-belief picture sequencing task; FPT, faux pas task; HC, healthy controls; JAT, joke-appreciation task; MA, meta-analysis; MASC, movie for the assessment of social cognition; MDD, major depressive disorder; MDE, major depressive episode; MET, multifaceted empathy test; MSAT, mental state attribution tasks; NTT, non-verbal ToM tasks; RMET, reading the mind in the eyes test; TASIT, the awareness of social inference test; ToM, theory of mind

* Corresponding author at: Department of Psychiatry and Psychotherapy, University of Pécs, Medical School, H-7623 Pécs, Rét u. 2., Hungary.
E-mail address: simon.maria@pte.hu (M. Simon).

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research paid increasing attention to BPD patients' social dysfunctions during the past decades, and a growing body of data indicates that BPD patients have social cognitive deficits (Daros et al., 2013; reviewed by Roepke et al, 2013; Herpentz and Bertsch, 2014.). Theory of mind (ToM), (or mentalizing) is one of the essential components of social cognition. ToM is the ability to attribute mental states (i.e. beliefs, desires) to self and others, and to understand and predict their behaviors, intentions, and wishes (Baron-Cohen, 1995).

Hence, ToM is a multidimensional construct involving several dimensions. Sabbagh (2004) identified two processes of ToM: (1) detecting and discriminating cues in the immediate social environment, i.e. the ability to *decode* the mental states of others; and (2) making inferences about those cues, i.e. the ability to *reason* about the mental states of others. An additional distinction can be made between components of ToM: one component is involved in understanding others' intentions and beliefs (*cognitive* or 'cold' ToM), whereas the other one processes other people's feelings and emotions (*affective,* or 'hot' ToM). The findings of the functional brain imaging studies sustain the separate neurological underpinnings of ToM decoding and reasoning, as well as those of cognitive and affective ToM (Shamay-Tsoory et al., 2006; Sabbagh 2004). During the past years, increasing attention has been paid to the disassociations of processes and components of ToM in specific clinical populations. Several studies found intact or enhanced mental state decoding abilities together with a dissociation between decoding and reasoning abilities in BPD samples (Preissler et al., 2010; Baez et al., 2015; Zabizadeh et al., 2017). Harari et al. (2010) found a dissociation between cognitive and affective ToM in patients with BPD, but this dissociation was not replicated in later studies (Baez et al., 2015; Petersen et al., 2016). Recently, two studies using different ToM tasks in the same sample reported a decoupling of mental state decoding and reasoning abilities, as well as that of affective and cognitive ToM in BPD (Baez et al., 2015; Zabizadeh et al, 2017).

Clinical studies report common comorbidities in the BPD populations: e.g. 41–83% for major depressive disorder (MDD), 10–20% for bipolarity, 64–66% for substance misuse, 46–56% for post-traumatic stress disorder (PTSD), 23–47% for social phobia, 16–25% for obsessive-compulsive disorder, 31–48% for panic disorder, and 29–53% for any eating disorder (Lieb et al., 2004; Zanarini et al., 1998). Among these, MDD and PTSD have been found to negatively influence ToM performance in BPD patients (e.g. Unoka et al., 2015; Zabizadeh et al. 2017; Nazarov et al., 2014).

Until now, several studies have investigated ToM in BPD, but the results were controversial. Discrepant findings on ToM deficits in BPD might be caused by the low sample sizes, the variability of the ToM processes and components assessed, as well as the heterogeneity of the clinical samples mainly due to the co-morbidities. To resolve controversies, we conducted a quantitative meta-analysis (MA) of the existing data on ToM in BPD. So far, two meta-analyses of social cognition in BPD have been published. Daros et al. (2013) reviewed and meta-analyzed data on facial emotion recognition in BPD – involving 10 primary studies, while Richmann and Unoka (2015) aggregated and meta-analyzed ToM results of 5 studies. However, the latter publication comprised only studies using the Reading the Mind in the Eyes Test (RMET, Baron-Cohen et al., 2001) to assess ToM in BPD.

We outlined the following meta-analysis questions: Can overall ToM deficits be detected in BPD patients compared to healthy control subjects in a large, pooled sample derived from several studies? If so, how can we characterize BPD patients' ToM deficits within the various dimensions and subcomponents of ToM? Do demographic and clinical variables have an impact on ToM capacities of BPD patients? Does task type have an impact on the ToM results? Are there tasks particularly sensitive to assess BPD patients' ToM abnormalities?

2. Methods

2.1. Literature search and study selection

PRISMA guideline (Moher et al., 2009) was followed when conducting this MA. In agreement with other meta-analyses on ToM deficits in psychiatric disorders (recently reviewed by Cotter et al., 2018), electronic, peer-reviewed databases including PubMed, Scopus, PsychINFO, and Web of Science (from January 1990 to November 2017) were searched using keywords {"Theory of mind" OR "mentalizing" OR "social cognition"}, AND {"borderline personality disorder"}. The reference list of papers examined for eligibility criteria, as well as that of reviews on social cognition in BPD, were also reviewed for additional publications.

The initial search strategy yielded 697 studies. After filtering duplicates, 445 studies were screened for eligibility criteria. Studies were selected if they (i) investigated ToM performances of patients with BPD fulfilling DSM-IV criteria confirmed by the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II, First et al., 1997]) (ii) included healthy comparison groups, (iii) used well-established, valid, and widely used ToM tests, and (iv) presented appropriate data to determine effect sizes and variances. All identified publications were reviewed and data were extracted by two authors (N.N. and M.S.) independently. Inconsistencies of study selection and data extraction were discussed. A discrepancy of data extraction appeared with regard to one publication (5%); nonetheless, it was resolvable: after discussion, there was a 100% agreement on data extraction.

Reasons for exclusion were: participants with no or with not sufficiently established diagnosis of BPD ($n = 4$), no healthy comparison group ($n = 4$), no eligible ToM tasks ($n = 3$), overlapping sample ($n = 1$), mixed clinical sample ($n = 2$). We did not include studies with adolescent samples ($n = 4$), because ToM skills are known to be developing during that age (Sharp et al., 2013; Blackmore 2012); therefore, adding adolescent samples to the MA with adults would have substantially increased the heterogeneity. Regarding the commonly co-occurring psychiatric comorbidities in BPD, samples with typical psychiatric comorbidities (e.g. MDD, PTSD, eating disorders, anxiety disorders, and other personality disorders) were not excluded from the meta-analysis. Fig. 1 presents the flowchart of the study selection process. We also contacted authors for unreported data and missing information.

Seventeen studies involving 585 patients with BPD, as well as 501 healthy controls (HC) passed the inclusion criteria (Table 1). There was no significant between-group difference for age ($d = –0.06$, $CI = –0.18$ to 0.06, $z = –0.97$, $p = 0.33$). The percentage of males was higher in the HC groups (11.99%) than in the BPD groups (9.2%), and there was a significant difference for gender between BPD and HC across the studies ($RR = 1.18$, 95% $CI = 1.04$ to 1.35, $z = 2.49$, $p < 0.05$). Therefore, gender was added as a moderator to the analysis.

2.2. ToM measures

The most frequently applied ToM task was the Reading the Mind in the Eyes Test (RMET, Baron-Cohen et al., 2001) that measures the ability of *mental state decoding* (N = 8). In RMET, a series of photos presenting only the eye region is shown, and participants are instructed to pick one from four words presented simultaneously with the eyes to best describe the emotional state of the person in the photo. However, partially based on neuroimaging studies, where RMET has been found to be related to amygdala activation (e.g. Russel et al, 2009), it is widely used as a measure of affective ToM as well.

Other tasks assessed the *mental state reasoning* abilities: Faux Pas Task (FPT, Stone et al., 1998) was used in 5 studies; in 2 other studies, ToM was measured with Happé's Advanced theory of mind test (ATT, Happé, 1994). In addition, several ToM cartoons, the Multifaceted Empathy Test (MET), the cognitive empathy subtest of which is

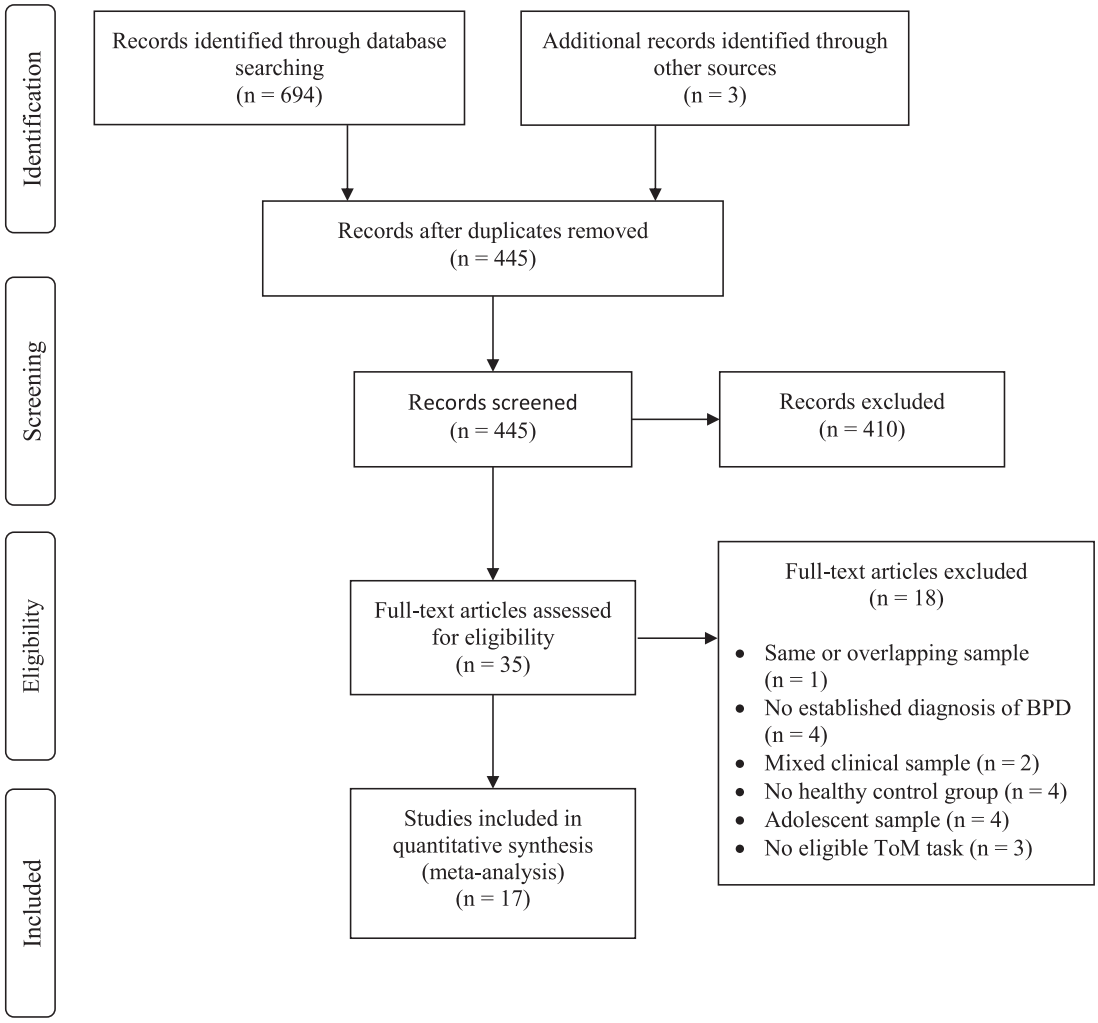

Fig. 1. Flowchart of the study selection process.

considered to measure affective ToM capacities (Dziobek et al., 2008), as well as the Movie for the Assessment of Social Cognition test, which is an ecologically valid, video-based ToM task (MASC, Dziobek et al., 2006) and an other video-based ToM test, the Awareness of Social Inference Test (TASIT, McDonald et al., 2003) were applied in the selected studies for measuring mental state reasoning.

For a subsequent analysis, we subgrouped the existing ToM data into cognitive and affective components of ToM. It is widely accepted in ToM research that specific ToM tests (or their subscores) are considered as measures of affective or cognitive ToM. There is agreement that RMET predominantly measures the capacity to understand others' emotions and feelings (e.g. Petersen et al., 2016; Zabizadeh et al. 2017), while false belief tests or ATT assess the capacity to understand others' beliefs and intentions. However, some more complex ToM tests (e.g. FPT, MASC, CAMS) contain questions for both affective and cognitive ToM. In case of the latter tests, if data were available, we calculated with the cognitive and affective scores separately. (***Supplementary Table 1*** presents the complete list of ToM tests and the subscores that were used for calculating affective and cognitive ToM).

2.3. Data analysis

We conducted a meta-analysis on the results from the different studies using an aggregate data approach. Negative effect sizes indicated poorer performance of the BPD group relative to the healthy group. For studies that reported more than one ToM task, within-study effect sizes and variances were aggregated by the Gleser and Olkin (1994) procedure. First, a meta-analysis for overall ToM was conducted using aggregated effect sizes across all studies.

Then, we performed separate categorical random-effects meta-analyses for the two main ToM processes: for mental state decoding (i.e. RMET only), and for mental state reasoning (any other ToM task used in the studies). Effect sizes for the different valences of RMET (neutral, positive, negative) were also counted.

Subsequently, meta-analyses of affective and cognitive ToM were performed ***(Supplementary Table 1)***. Then, MAs for predominantly verbal, visual, and multimodal ToM tasks were conducted. If there were at least 4 studies reporting data on a particular task, then a separate, task-specific MA was also conducted (Fu et al., 2011). Individual task analysis was possible for FPT (n = 5). In addition, effect sizes for RMET (n = 8, as mental state decoding), cartoons (contents differ, n = 4), as well as for MASC (n = 4) were calculated.

All statistical analyses were performed in R environment (R Development Core Team, 2015; Del Re and Hoyt, 2010) with the Metafor (Viechtbauer, 2010) and the MAd packages (Del Re and Hoyt, 2010). Effect sizes were weighted using the inverse variance method. Because studies in the MA are not supposed to share a common effect size, random effects model with DerSimonian–Laird estimate was used to calculate summary effect sizes (DerSimonian and Laird, 1986). The homogeneity of the distribution of the weighted effect sizes was examined with the Q and I^2 tests (Hedges and Olkin, 1985). Between-study heterogeneity in the random effects model was estimated with

Table 1
Characteristics of included studies.

BPD = Patients with borderline personality disorder, **HC** = Healthy controls, **ToM** = Theory of mind, **MDD** = Major depressive disorder, **PTSD** = Posttraumatic stress disorder, **Edu** = Educational level, **ATT** = Happé's advanced theory of mind test, **RMET** = Reading the mind in the eyes test, **FPT** = Faux pas test, **MSAT** = Mental state attribution tasks (Brüne, 2005), **MASC** = Movie for the assessment of social cognition, **MET** = Multifaceted empathy test, cognitive empathy score, **JAT** = ``Joke-appreciation" task, **EAT** = Shortened version of the expression attribution test (Langdon et al., 2006), **FBPST** = False-belief picture-sequencing tasks (Langdon and Coltheart, 1999), **CAMS** = Cartoon-based assessment of mentalizing skills (Dimaggio and Brüne, 2010); **NTT**: Non-verbal ToM tasks (Happé et al., 1999; Gallagher et al., 2000), **TASIT**: The awareness of social inference test.

				Characteristics of BPD group				
Study	Sample (female) BPD–HC	Matched for	ToM tasks	Mean age	MDD% *(lifetime)*	PTSD%	Medication status	Outcome
Arntz et al. (2009)	16(16)–28(28)	Age, gender, IQ	ATT	30.5	–	–	–	No difference
Fertuck et al. (2009)	30(26)–25(15)	Age, edu	RMET	29.8	56.7 *(76.7)*	30	13.3%	BPD > HC
Harari et al. (2010)	20(18)–22(19)	Age, edu gender, IQ	FPT	32.1	0	0	–	FP recognition, cognitive FP: BPD < HC, affective FP: no difference
Ghiassi et al. (2010)	50(46)–20(13)	Age	MSAT	26.2	–	–	majority of the sample	No difference
Preissler et al, (2010)	64(64)–38(38)	Age, gender, IQ	MASC, RMET	29.2	12.5 *(42.2)*	35.9	32.8%	MASC: BPD < HC RMET: no difference
Dziobek et al. (2011)	21(21)–21(21)	Age, gender, IQ	MET	31.7	19 *(28.6)*	38.1	–	BPD < HC
Schilling et al. (2012)	31(30)–27 (12)	Age, edu	RMET	27.3	67.7	16.1	80.6%	No difference
Frick et al. (2012)	21(21)–20(20)	Age edu, gender	RMET	21.7	23.8 *(47.6)*	33.3	0%	BPD > HC
Wingenfeld et al. (2014)	38(38)–35(35)	Age, gender	MASC, MET	24.3	23.7	13.2	0%	No difference
Unoka et al. (2015)	78(74)–76(69)	Age, edu gender	RMET	29.9	43.6	5.1	majority of the sample	BPD < HC
Vaskinn et al. (2015)	25(25)–25(25)	Age, edu, gender	MASC	30.7	52	12	–	No difference in overall score (overmentalizing errors: BPD > HC)
Baez et al. (2015)	15(12)–15(13)	Age, edu gender	FPT, RMET	38.4	26.7	–	–	FP: BPD > HC RMET: no difference
Andreou et al. (2015)	44(38)–38(22)	Age	MASC	29	61,4	0	–	BPD < HC (overmentalizing errors)
Petersen et al. (2016)	19(18)–20(19)	Age, gender, IQ	RMET, JAT, FPT, EAT, FBPST	32.5	0	52	94.7%	BPD < HC only in more complex tasks (FP, JAT)
Brüne et al. (2016)	30(30)–30(30)	Age, edu, gender	CAMS	25.7	–	–	63.3%	BPD < HC
Yeh et al. (2017)	40(37)–36(33)	Age, edu, gender	FPT, ATT, NTT, TASIT	30.9	–	–	–	NTT, TASIT: BPD < HC ATT, FP: no difference
Zabihzadeh et al. (2017)	44(21)–25(12)	Age, edu, gender, IQ	RMET, FPT	26.2	50	34.1	–	RMET: BPD only > BPD + MDD > HC FP: HC > BPD only > BPD + MDD

tau-squared (τ^2), an estimate of the total amount of heterogeneity.

Publication bias was estimated with the Fail-safe N test, and tests for assessing funnel plot asymmetry. Fail-safe N test computes a pooled p-value for all studies in the MA and calculates how many further studies with a zero effect would be necessary to generate a non-significant p. Egger's test and Begg and Mazumdar's test rely on the assumption that studies with small sample sizes are more often published if they report significant results, while studies with large sample sizes are usually published regardless of significant findings.

Meta-regression analyses were conducted for age, gender (the ratio of females in the BPD group compared to that in the HC group), and education (years), as well as for clinical comorbidities (current MDD, anxiety disorders [=panic disorder + phobias + generalized anxiety disorder], social phobia, PTSD, any eating disorder, and substance use disorder) (***Supplementary Table 2)***. Other personality disorders, symptom severity of current depression, childhood trauma, and neurocognitive functions were also considered, but there were no sufficient data available to add them to the analysis. In the moderator analyses, we used study-level continuous measures only when they were published in at least 7 studies (Fu et al., 2011). Categorical subgroup variables were used only when each subgroup had a minimum of 4 studies (Fu et al., 2011). For continuous moderators, analyses with a linear mixed effects model, for categorical variables, subgroup analyses were conducted. Q_{bet}-test was used to compare the effect sizes of the subgroups (Borenstein et al., 2009).

3. Results

The summary of the main meta-analysis results is presented in *Table 2**, and Supplementary Fig. 1***. (Negative effect sizes indicates poorer performance of the BPD group.)

3.1. Overall ToM

Overall ToM performance (n = 17) was significantly impaired in the BPD group compared with the HC group, but the effect size was low (d = − 0.2, p = 0.01) (Fig. 2, Table 2). Because there was high heterogeneity for the distribution of effect sizes for the total ToM score, further moderator analyses were conducted. No publication bias was found.

3.2. Mental state decoding versus reasoning

Mental state decoding (separate analysis of RMET only, n = 8): We found no significant effect size for overall accuracy in RMET (d = 0.12, p = 0.55). The distribution of the effect sizes was significantly heterogeneous (Fig. 3, Table 2). Data on RMET were further analyzed for valence types (positive, negative, and neutral, n = 7). Results showed no significant between-group differences for positive (d = − 0.02), and for neutral valences (d = − 0.33); heterogeneities were significant. Nevertheless, there was a trend level significant difference between BPD patients and HCs for the negative valence: d = 0.7 (p = 0.07, heterogeneity was significant) (***Supplementary Fig. 2)***.

Mental state reasoning abilities were significantly impaired in BPD (d = − 0.61, p < 0.001, n = 13) (Fig. 4, Table 2).

BPD patients' mental state reasoning deficits were more robust compared to the mental state decoding abilities (Q_{bet} = 9.89, p < 0.05, n = 13 + 8).

3.3. Affective versus cognitive toM

Affective ToM (n = 12): Patients with BPD did not differ in their affective ToM abilities compared to HCs (d = − 0.17) (Fig. 5). After removing RMET data from data on affective ToM, we calculated an effect size for the 'affective ToM without RMET' subgroup. ***(Supplementary Fig. 3)*** Here, we found that BPD patients significantly underperformed HC in affective ToM tests (n = 7, d = −0.62, p < 0.001), if RMET data (i.e. data of affective decoding or discrimination) were removed from the subset of affective ToM data.

Cognitive ToM (n = 9): Patients with BPD performed significantly worse in cognitive ToM tasks (d = − 0.44, p = 0.01) (Fig. 6, Table 2).

However, there was no significant difference between BPD patients overall affective and cognitive ToM deficits (Q_{bet} = 1.54, df = 1,p = 0.21, n = 12 + 9.). Similarly, there was no significant difference between affective Tom without RMET and cognitive ToM (Q_{bet} = 1.06, p = 0.3, n = 7 + 9).

3.4. The effect of task types

We reanalysed data by task types, and calculated effect sizes for predominantly visual (n = 13, d = − 0.14, p = 0.36), verbal (n = 6, d = − 0.81, p = 0.01), and multimodal (i.e. video-based; n = 5, d = − 0.52, p < 0.001) ToM tasks. The comparison of performances in

Table 2
Mean weighted effect sizes for differences between patients with BPD and healthy controls on ToM.

ToM test	*St. N*	BPD *N*	HC *N*	*d*	95% CI	*z*	*p*	Q-test (*p*)	τ^2	Egger (*p*)	Begg (*p*)	Fail safe N
ToM total	17	585	501	**−0.27**	−0.48, - 0.06	−2.56	**0.01**	<0.0001	0.13	0.09	0.09	134
ToM process												
Decoding (=RMET)	8	302	246	0.12	−0.28, 0.51	0.59	0.55	<0.0001	0.25	0.31	0.40	N.A.
Positive	7	287	231	−0.008	−0.43, 0.41	−0.04	0.97	0.004	0.26	0.34	0.38	N.A.
Neutral	7	287	231	−0.33	−0.97, 0.31	−1.01	0.91	<0.0001	0.66	0.96	0.77	N.A.
Negative	7	287	231	0.7	−0.06, 1.46	1.8	0.07	<0.0001	0.97	0.1	0.07	N.A.
Reasoning	13	425	353	**−0.61**	−0.87, −0.35	−4.60	**<0.0001**	<0.0001	0.16	0.62	0.59	244
ToM content												
Affective ToM	12	410	354	−0.17	−0.48, 0.15	−1.03	0.30	<0.0001	0.24	0.53	1.00	N.A.
Aff. ToM without RMET	7	206	181	**−0.62**	−0.87, −0.38	−4.95	**<0.0001**	0.18	0.04	0.09	0.24	57
Cognitive ToM	9	290	244	**−0.44**	−0.71, −0.17	−3.20	**0.001**	0.007	0.10	0.88	0.46	57
Task type												
Visual	13	481	388	−0.14	−0.44, 0.16	−0.93	0.36	<0.0001	0.23	0.26	0.25	N.A.
RMET (=decoding)	8	302	246	0.12	−0.28, 0.51	0.59	0.55	<0.0001	0.25	0.31	0.40	N.A.
Cartoons	4	139	106	**−0.59**	−0.88, −0.31	−4.09	**<0.0001**	0.24	0.02	0.48	0.75	22
Verbal	6	154	146	**−0.81**	−1.46, −0.17	−2.48	**0.01**	<0.0001	0.55	0.49	0.72	55
Faux pas task	5	138	116	**−1.07**	−1.65, −0.5	−3.68	**0.0002**	0.0008	0.33	0.33	0.48	69
Videos	5	209	172	**−0.52**	−0.79, −0.25	−3.74	**0.0002**	0.09	0.05	0.80	1.00	33
MASC	4	169	136	**−0.46**	−0.77, −015	−2.92	**0.0035**	0.09	0.05	1.00	1.00	16

ToM = Theory of mind, St.= Studies, BPD = Borderline personality disorder, HC = Healthy controls, d = Cohen's d, RMET = Reading the mind in the eyes test, MASC = Movie for the assessment of social cognition test.

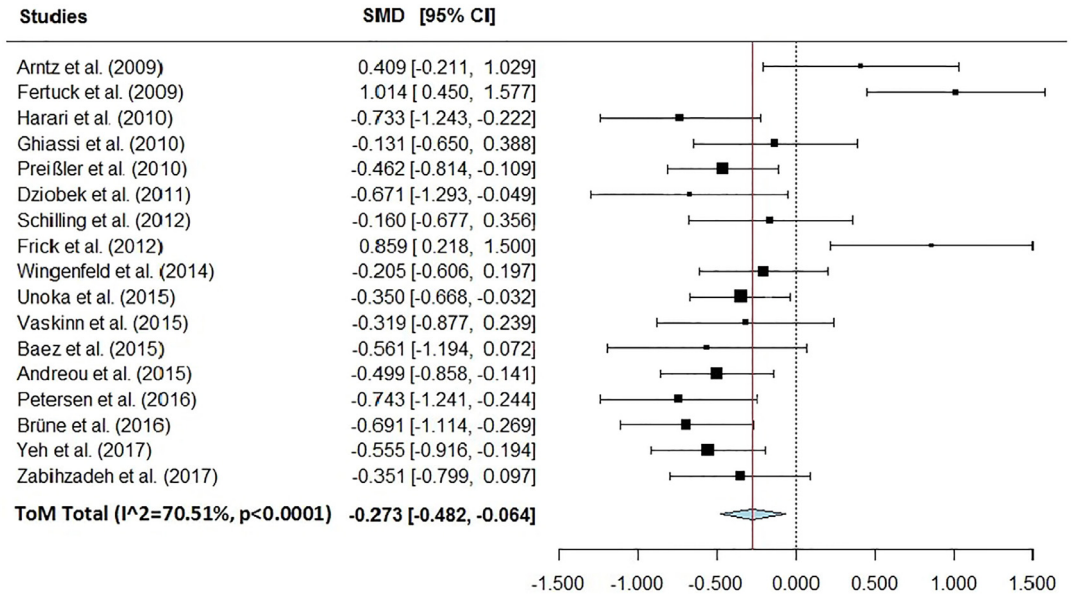

Fig. 2. Forest plot for meta-analysis of overall ToM (theory of mind) in BPD (borderline personality disorder). Negative effect size indicates poorer performance of the BPD group. .

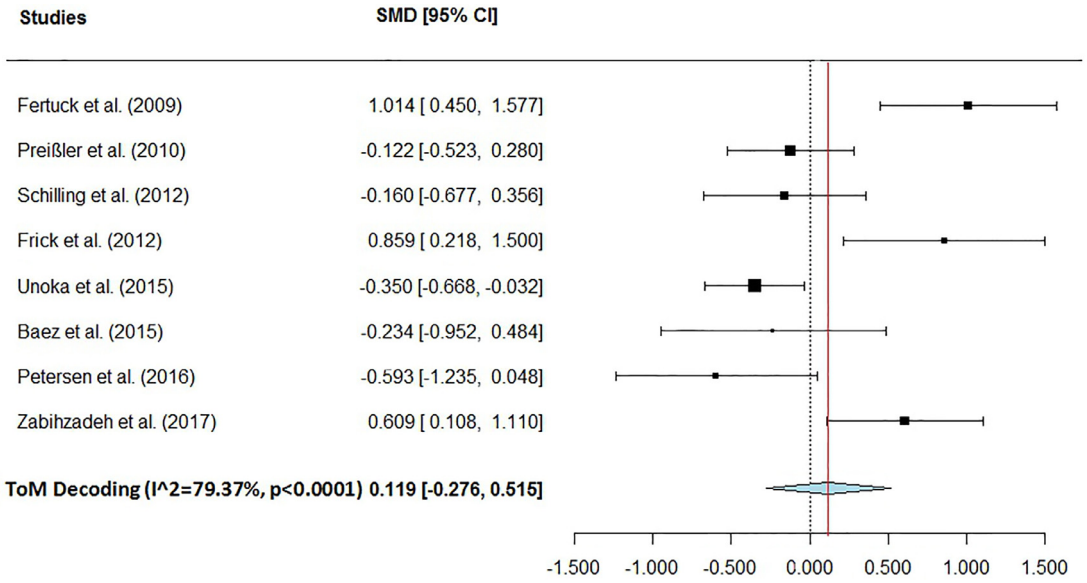

Fig. 3. Forest plot for meta-analysis of mental state decoding in BPD (borderline personality disorder). Negative effect size indicates poorer performance of the BPD group.

the three task types revealed that BPD patients performed significantly worse in verbal than in visual tasks ($Q_{bet} = 4.61$, $p < 0.05$). (Table 2).

To explore the origin of BPD patients' relatively good performance in visual tasks, we ran a separate MA with data of visual tests without RMET (i.e. cartoons and MET, $n = 6$)), and found a significant effect size: $d = -0.54$, $p < 0.001$, *95% of CI*: -0.76 to -0.33, $z = -4.83$, $I^2 = 16.34\%$, $\tau^2 = 0.012$. The heterogeneity was substantially reduced compared with the MA of the composite visual tests. BPD patients' ToM deficit in visual tasks without RMET was more robust compared to that in RMET ($Q_{bet} = 6.7$, $p = 0.01$, $n = 8 + 6$).

In individual task analyses, there was no significant deficit in BPD patients' accuracy in RMET $d = 0.12$ ($n = 8$, see above by mental state decoding); however, there were significant impairments of BPD patients in performing the FPT ($d = -1.07$, $p < 0.001$, $n = 5$), the ToM cartoons ($d = -0.59$, $p < 0.001$, $n = 4$), as well as the MASC ($d = -0.46$, $p < 0.001$, $n = 4$). (Table 2) When comparing ToM impairments in the individual task types pairwise with post hoc Holm-modified Tukey procedure, we detected significant difference only between the RMET and FPT ($d = 1.18 \pm 0.29$, $z = 4.12$, $p < 0.001$).

3.5. Meta-regression analyses

In the meta-regression analyses, there was no moderating effect of age, education, and gender (the ratio of females in the BPD group compared to that in the HC group). However, the summed rate of panic disorder, generalized anxiety disorder, and phobias ($n = 9$) had a significant positive effect on BPD patients' ToM performance compared to HC ($z = 2.11$, $p < 0.035$, the proportion of total between-study variance explained by model: $R^2 = 0.32$). Also, the summed prevalence rate of panic, generalized anxiety disorders and any phobias ($n = 9$)

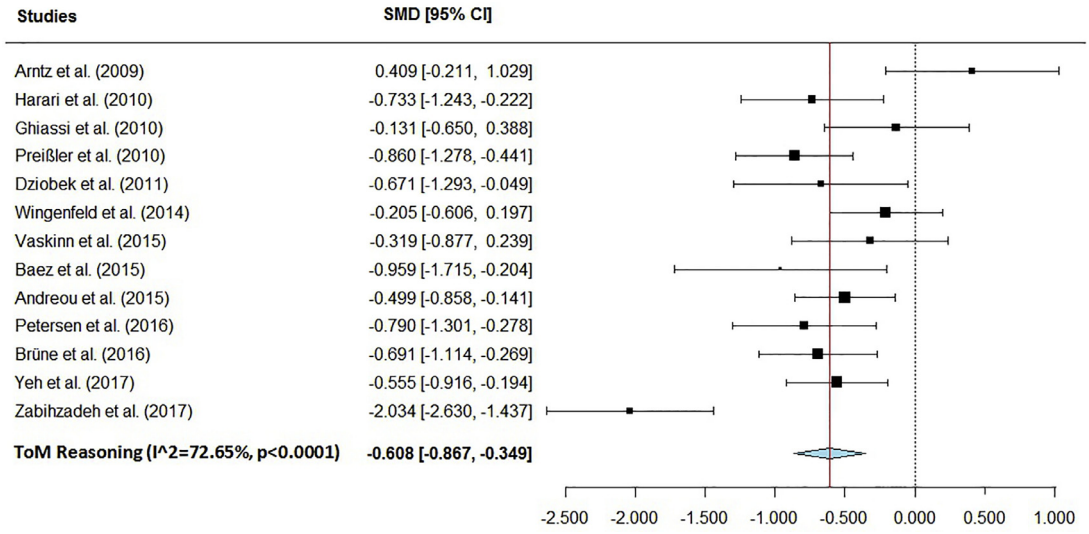

Fig. 4. Forest plot for meta-analysis of mental state reasoning capacities in BPD (borderline personality disorder). Negative effect size indicates poorer performance of the BPD group.

had a significant positive effect on BPD patients' affective ToM performance compared to HC ($z = 2.06$, $p < 0.04$, the proportion of total between-study variance explained by model: $R^2 = 0.34$). There was no other significant relationship between any other comorbidity variables and ToM performances.

4. Discussion

4.1. Main results

The main finding of our MA is that BPD patients are significantly impaired in their overall ToM capacities compared to HC; however, the effect size was relatively small.

Another important finding of the present study is that BPD patients' mental state decoding capacities (measured by RMET) do not significantly differ from those of HCs. In contrast, BPD patients' mental state reasoning was found to be significantly worse compared to HC subjects. Q_{bet} test revealed that deficits of the mental state reasoning were significantly poorer than those of mental state decoding in BPD (***Supplementary Fig. 1***).

RMET contains subtle emotional information that taps a wider range of mental states beyond the basic emotions. However, during RMET, participants should put themselves into the situation of the person presented in the photograph, therefore RMET assesses ToM capacities. Requiring no inferences about cognitive and affective mental contents, as well as no contextual processing, RMET is regarded as an appropriate task to measure the initial, decoding (or discriminating) ToM processes, predominantly the decoding of subtle facial affective cues. A recent MA collapsing RMET performances across 5 studies reported significantly impaired RMET accuracy in neutral valences in BPD patients, while co-occurring MDD enhanced their performance in general, and on positive valence scores (Richman and Unoka, 2015). In our more extended MA ($n = 8$), we could not replicate this finding: we found no moderating effect of the current major depressive episode (MDE), and only BDP patients' slightly enhanced accuracy in negative valences could be detected (significant at the trend level).

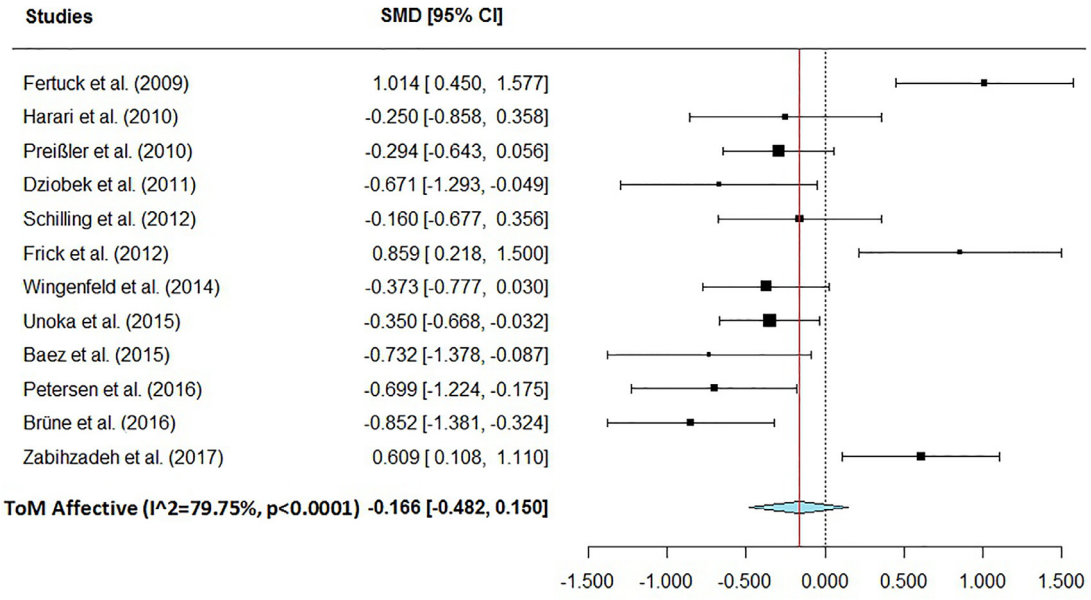

Fig. 5. Forest plot for meta-analysis of affective ToM (theory of mind) in BPD (borderline personality disorder). Negative effect size indicates poorer performance of the BPD group.

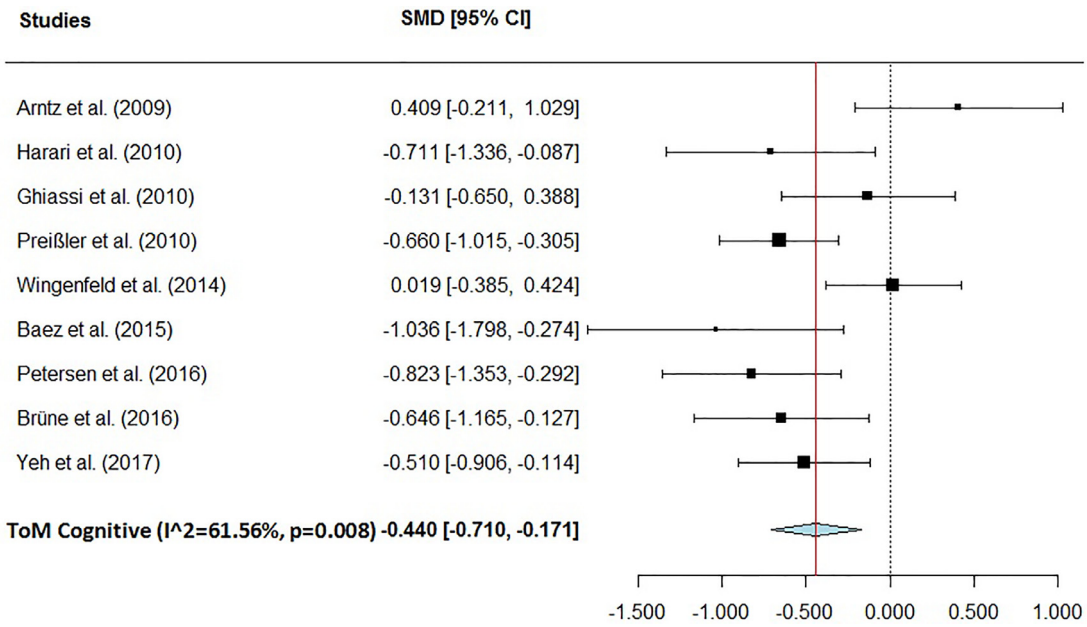

Fig. 6. Forest plot for meta-analysis of cognitive ToM (theory of mind) in BPD (borderline personality disorder). Negative effect size indicates poorer performance of the BPD group.

The latter result is in accord with theories about BPD patients' sensitivity to negative stimuli, which seems to be characteristic of BPD independently of co-existing depression. BPD patients' relative sensitivity for other peoples' negative mental states is in agreement with the amygdalar hyper-reactivity and altered functional connectivity observed in functional neuroimaging studies during RMET and facial emotion recognition tasks (Frick et al., 2012; Donegan et al., 2003; Minzenberg et al., 2007; Cullen et al., 2011). Our results also fit well to the theory of Fonagy and Bateman (2008): BPD patients who grow up in a non-reflecting, non-validating, and often abusing family environment develop an increased emotional vigilance to social stimuli, especially to those with negative emotional content. Nevertheless, BPD patients' ToM abilities are just partially developed, since their reflexive awareness is low, and their mental state reasoning abilities are significantly impaired.

However, findings with RMET in BPD were rather inconsistent, which was basically due to three studies: in each, BPD patients overperformed normal controls. The first study by Frick et al. (2012) comprised only non-medicated females with a relatively low BDI score and less severe comorbid psychopathology in the BPD group. The second study by Fetruck et al. (2009) recruited patients from the acute setting with more severe co-morbid psychopathologies including numerous suicide attempters. Here, the percentage of males was significantly higher in the HC than in the BPD group. In the third study by Zabizadeh et al. (2017), 50% of the BPD patients suffered from clinically relevant MDD, and the patients were recruited mainly from the acute settings. In this study, the proportion of males was exceptionally high but there were no between-group differences in gender ratio. In sum, neither the setting where the patients were recruited, nor the severity of the comorbid psychiatric pathologies, nor the gender ratio of the groups could ultimately explain the relatively good performance of the BPD groups in these studies. Thus, our present MA proposes that the between-study variability of the RMET results seems to be multifactorial, as no consistent reason for the heterogeneous RMET performances could be found. Finally, although no data are available, one cannot exclude the hypothetical role of subtle between-study differences of RMET procedure that could contribute to the extent to which studies implicitly activated a reasoning component to the decoding task.

Furthermore, we detected BPD patients' impaired cognitive ToM capacities, while their affective ToM abilities were relatively preserved. Based on that, one can presume that BPD patients' interpersonal difficulties are mainly due to their deficits in cognitive ToM. This finding can be in agreement with the theoretical framework of the dissociability of affective and cognitive mentalization (Fonagy et al., 2012). Fonagy and Bateman indicate that different forms of psychopathological states are related to the inhibition, deactivation, or simply dysfunction of either the cognitive or the affective or both aspects of mentalization. Patients with BPD are typically overwhelmed by automatic and affect-driven mentalizing, but they have difficulties in integrating the affective experiences with reflective and cognitive knowledge. Nevertheless, the latter clinical observation can be in line with our meta-analysis of affective ToM subgroups. After reanalyzing our affective ToM data without RMET, we found that BPD patients significantly underperformed HC in affective ToM tasks. Accordingly, we can suppose, that BPD patients relatively intact affective ToM capacities are attributable to their affective decoding and discriminating capacities measured by RMET.

However, when we compared BPD patients' cognitive and overall affective ToM deficits with Q_{bet} test, BPD patients' cognitive ToM deficits were not significantly worse than that of their overall affective ToM. Notably, we got a similar result when we compared affective ToM without RMET with cognitive ToM. Thus, we should carefully interpret our MA results with affective and cognitive ToM, especially because the number of studies that published affective and cognitive ToM scores separately was low. Future research with simultaneous affective and cognitive ToM measures is needed to understand the exact nature of dissociation of affective and cognitive ToM in BPD.

4.1. The effect of comorbidities on ToM in BPD

The summed rate of DSM-5 anxiety disorders (primarily panic disorder, agoraphobia, specific phobia, social anxiety disorder, and generalized anxiety disorder) has been proofed to have a positive effect on BPD patients' overall ToM performance and their affective ToM abilities. Among the anxiety disorders, social anxiety disorder presents most typically social dysfunctions and interpersonal difficulties. In a handful of studies that have been published so far, patients with social anxiety disorder were found to have various deficits of ToM decoding and reasoning (Washburn et al., 2016; Buhlmann et al., 2015; Hezel and

McNally, 2014). Interestingly, no significant relationship could be detected between comorbid social anxiety disorder and ToM in our MA. Similarly to the summed prevalence of anxiety disorders, only study-level data (from 9 studies) were available, with no measures of current, individual symptom severity.

A very recent study reported that patients with generalized anxiety disorder displayed more accurate mental state reasoning capacities compared to HC, especially when they suffered from an increased worry (Zainal and Newman, 2017). Although there are no data in the literature about ToM capacities in panic disorder, agoraphobia, or simple phobia, one can assume that worry, concern, and continuous anticipatory anxiety can induce a state of hypervigilance, where people have an increased need for contact with and support from others. These factors might enhance BPD patients' interpersonal sensitivity and ToM capacities if they have comorbid anxiety disorders. Nevertheless, further research is needed to specify the effect of comorbid anxiety disorders in BPD on ToM capacities.

In contrast to previous findings in BPD patients with comorbid depression, our meta-regression analyses did not reveal any effect of comorbid MDD, neither on overall ToM performance nor on any other ToM dimensions or components. There is some evidence for enhanced ToM abilities in non-clinical samples with dysphoria (measured by Beck depression inventory, dysphoria scored > 12) (Harkness et al., 2005; Harkness et al., 2010). Nonetheless, no studies included in our MA measured subthreshold or subclinical depression.

4.2. The effect of task type

Verbal and multimodal task types revealed significantly impaired ToM in BPD. For visual tasks, however, there was no significant difference between BPD patients' and HCs' ToM performance. Presumably, the latter result was due to the effect of RMET. When visual tasks were reanalyzed without RMET, BPD patients were found to be significantly impaired in visual tasks. In addition, BPD patients showed significantly fewer impairments in RMET than in other visual tasks (i.e. cartoons + MET).

Meta-analyses results of individual task types were more consistent than those of subgroups by the predominant modality of stimuli, and revealed, that except RMET, all other test types detected ToM deficits in BPD patients. The largest effect size was found with the FPT, while MA for overall verbal tasks, cartoons with different content, movies, and MASC yielded medium effect sizes.

Accordingly, the FPT seems to be the most demanding ToM task for BPD patients. FPT (Stone et al., 1998) comprises stories describing complex social situations, where a character commits a conversational failure by saying something (s)he should not say or saying something awkward. The FPT encompasses high contextual demands and requires implicit integration of cognitive inferences about mental states. Moreover, the FPT is purely verbal, thus patients with BPD cannot rely on their enhanced sensitivity to non-verbal emotional stimuli while performing the FPT.

Several types of ToM cartoons were used in studies involved in our MA, in which participants needed understand social situations presented in the cartoons and represent the characters' mind, in order to find chronological order, or understand irony, humor, and false beliefs. BPD patients were found to underperform HCs in more complex cartoon tasks (e.g. CAMS, Dimaggio and Brüne, 2010; or JAT, Langdon et al. 2006) where not only cartoon sequencing but a subsequent answering of questions about the cartoon characters' mental states, or integration of multiple perspectives to decipher humour were also required (Brüne et al., 2016; Petersen et al., 2016).

In sum, all tasks with a higher level of complexity detected ToM impairments in BPD patients. In BPD research, several authors emphasize the importance of ToM tasks with high ecological validity (Minzenberg et al., 2006; Dyck et al., 2009; Baez et al., 2015; Roepke et al., 2013). Displaying real-life situations, the multifaceted empathy test (MET), as well as the video-based ToM tasks (MASC, TASIT), are regarded as ecologically valid. Especially, video-based tasks entail the integration of several cues from faces, gestures, and prosody, along with those of the social context. Of note, MASC is unique, because it measures several forms of mentalizing errors (i.e. hypomentalizing, hypermentalizing). So far, only 4 studies have used MASC in ToM research in adults with BPD. Further research is recommended using MASC in BPD patients to evaluate how sensitively MASC detects specific hypermentalizing tendencies in BPD.

4.3. Limitations

Unexpectedly, meta-regression analyses revealed no moderating effect of the comorbid MDE and PTSD. Since no sufficient data on the individual symptom severity of depression were available, we conducted the analyses with study-level data. Hence, it was not possible to disentangle or weight the effect of mild and severe comorbid depression on ToM. Neither, we detected the moderating effect of comorbid PTSD. Similarly to MDE, only the percentage of comorbid PTSD in the samples, but no other clinical variables (such as symptom severity, chronicity or acuteness, co-occurrence with dissociative symptoms, time and nature of the traumatic event, etc.) were available. There is increasing evidence that adverse childhood life events and insecure attachment play a crucial role in BPD patients' mentalizing deficits (Fonagy et al., 2003). Unfortunately, only a few studies included in the MA quantified the quality of parental care or the severity of adverse childhood life events in BPD patients (e.g. Ghiassi et al., 2010; Brüne et al., 2016, Petersen et al., 2016).

The missing data on medications made it impossible to analyze and reveal any medication effect on ToM impairments. Furthermore, only one study in our MA assessed BPD patients' neurocognitive functions, and their correlation with ToM performances (Baez et al., 2015), therefore the impact of neurocognitive functions on ToM could not be evaluated.

Only 4 studies measured mental state decoding and reasoning in the same sample simultaneously, therefore it was not possible to compare data only from studies with simultaneous measures. So we performed the Q_{bet} test with all studies for mental state decoding ($n = 8$), and reasoning ($n = 13$). Although samples partially overlap, we present this result, because the *95%CI* of effect sizes showed no overlap. Nevertheless, this is an obvious limitation and requires revision in the future, when more simultaneous measures are available.

4.4. Conclusion

We demonstrate here that BPD patients have overall ToM deficits compared to HC. We also found that BPD patients have cognitive ToM impairments and deficits of mental state reasoning. This is in line with empiric clinical data on psychotherapeutic interventions in BPD: psychotherapeutic interventions are most effective if they target BPD patients' mental state reasoning and cognitive ToM.

Conflict of interest

There is no conflict of interest concerning the authors in conducting this study and preparing the manuscript.

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Contributors

Study design: Nándor Németh, Mária Simon, Boldizsár Czéh, Péter Hegyi.

Data collection, analysis, and interpretation: Nándor Németh, Mária Simon, Péer Hegyi.

Drafting of the manuscript: Mária Simon, Boldizsár Czéh, Nándor Németh.

Critical revision of the manuscript: all co-authors.

Approval of the final version for publication: all co-authors.

Supplementary materials

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Examining the Influence of Early Life Stress on Serum Lipid Profiles and Cognitive Functioning in Depressed Patients

Ágnes Péterfalvi[1,2†], Nándor Németh[1†], Róbert Herczeg[3], Tamás Tényi[4], Attila Miseta[2], Boldizsár Czéh[1,2] and Maria Simon[1,4]*

[1] Neurobiology of Stress Research Group, Szentágothai Research Centre, University of Pécs, Pécs, Hungary, [2] Department of Laboratory Medicine, Medical School, University of Pécs, Pécs, Hungary, [3] Bioinformatics Research Group, Szentágothai Research Centre, University of Pécs, Pécs, Hungary, [4] Department of Psychiatry and Psychotherapy, Medical School, University of Pécs, Pécs, Hungary

Background: Early childhood adversity is a strong predictor of the development of major depressive disorder (MDD), but not all depressed patients experience early life stress (ELS). Cardio-metabolic diseases and cognitive deficits often coincide in MDD and worsen its course and outcome. Adverse childhood experiences have been associated with elevated risk for cardiovascular disease (CVD), but little is known on the impact of ELS on cardiovascular risk factors in MDD. Here, we examined MDD patients with and without ELS to explore the effects of ELS on serum lipid and lipoprotein levels and on cognitive performances of the patients.

Methods: Participants with a mean age of 35 years (18–55 years) were recruited from the university mental health clinic and general community. Three groups, matched in age, gender and lifestyle were examined: MDD patients with ELS (n = 21), MDD patients without ELS (n = 21), and healthy controls (n = 20). The following CVD risk factors were assessed: serum lipids (total cholesterol, triglycerides, high- and low-density lipoproteins), body mass index and exercise in a typical week. MDD severity was measured by the Beck Depression Inventory. Childhood Trauma Questionnaire was used to assess early life adversities. Executive functions and attentional processes were assessed by the Wisconsin Card Sorting and Conners' Continuous Performance tests.

Results: Major depressive disorder patients with ELS had higher serum triglyceride and lower HDL-cholesterol concentrations compared to MDD patients without ELS. Linear regression analysis revealed that the severity of ELS had a significant negative association with HDL-cholesterol levels and significant positive associations with the serum levels of TG and TC/HDL-cholesterol index. We also found significant associations between some specific trauma types and lipid profiles. Finally, we could detect significant associations between depression severity and specific domains of the cognitive tests as well as between lipid profiles and certain domains of the Wisconsin Card Sorting Test. However, we could not detect any association between the severity of ELS and cognitive performance.

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****Correspondence:***
Maria Simon
simon.maria@pte.hu

[†] These authors have contributed equally to this work

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Conclusion: After controlling for depressive symptom severity and lifestyle variables, ELS was found to be a strong predictor of serum lipid alterations. Several, inter-correlated pathways may mediate the undesirable effects of ELS on the course and outcome of MDD.

Keywords: adverse childhood experience, childhood adversity, cardiovascular risk, cholesterol, depression, HDL, major depressive disorder, triglyceride

INTRODUCTION

Major depressive disorder is a key public health concern today (Kessler, 2012), as it is a commonly occurring and an often recurring condition associated with considerable functional impairments, diminished quality of life, increased medical morbidity, and mortality (Kessler and Bromet, 2013). MDD often coincides with somatic illnesses such as metabolic syndrome (Pan et al., 2012) and CVD (Hare et al., 2014); nevertheless, the direction of the causal relationship between depression and cardio-metabolic diseases, as well as the specific underlying mechanisms, have not yet been fully understood. Moreover, patients suffering from MDD often present neurocognitive deficits (Austin et al., 2001; McDermott and Ebmeier, 2009; Lee et al., 2012; McIntyre et al., 2013; Rock et al., 2014).

Major depressive disorder is a clinically heterogeneous disorder, which is a result of manifold etiological factors, as well as developmental pathways. ELS, such as adverse childhood experiences (ACEs) (e.g., physical, emotional, and sexual abuse, neglect, parental loss, and poverty), have long been known to be strong predictors of MDD in adulthood (e.g., Widom et al., 2007; Norman et al., 2012; Lindert et al., 2014). A recent meta-analysis of 26 studies revealed that childhood emotional abuse and neglect showed the strongest association with depression risk in adults, while sexual/physical abuse or family violence have been proved to be non-specific risk factors for various mental disorders (Mandelli et al., 2015). Adult MDD with prior ELS is associated with earlier onset, more severe symptomatology, a greater number and longer duration of depressive episodes, a tendency to be chronic or therapy-resistant, higher rates of psychiatric comorbidities, as well as suicidal behavior or impulsivity compared to MDD without ELS (Brodsky et al., 2001; Zlotnick et al., 2001; Klein et al., 2009; Wiersma et al., 2009; Hovens et al., 2010; Miniati et al., 2010; Nanni et al., 2012). Moreover, ELS is also a risk factor for severe metabolic alterations and central obesity (Pervanidou and Chrousos, 2012; Davis et al., 2014) and CVD (Rich-Edwards et al., 2012; Loria et al., 2014). Furthermore, a recent study which analyzed data on cardio-metabolic markers of 9000 cohort members found that physical and sexual abuse was associated with high LDL-C and low serum levels of HDL-C, and that childhood neglect, as well as emotional abuse, was associated with raised TG and lower HDL-C (Li et al., 2019). In sum, ELS appears to be related to adult cardio-metabolic complications and comorbidities by two etiologic mechanisms: (1) the direct effect of early and late life stress; (2) general factors that are compensatory behaviors, as well as attempts at self-help by food and agents (Kesebir, 2014).

Serum lipid concentrations have been widely investigated in MDD, however, studies yielded inconsistent results. Both higher (Ledochowski et al., 2003; Nakao and Yano, 2004; Moreira et al., 2017) and lower serum TC levels (Olusi and Fido, 1996; Maes et al., 1997; Ong et al., 2016) were registered in patients with MDD compared to controls, and null findings have also been reported (Lehto et al., 2008; van Reedt Dortland et al., 2010; Enko et al., 2018). Alterations of serum concentrations of LDL-C were most widely studied in MDD. Recently, a comprehensive meta-analysis found significantly lower cross-sectional LDL-C serum concentrations in MDD compared to HCs, when LDL-C was modeled as a continuous measure (Persons and Fiedorowicz, 2016). The authors suggested a U-shaped relationship between depression severity and LDL-C. Nevertheless, this meta-analysis did not consider the effect of ELS on LDL-C concentration in depression. Studies that investigated the relationship between HDL-C and MDD had produced contradictory findings. Some studies found no association at all (Aijänseppä et al., 2002; Rice et al., 2010), while others revealed a correlation between lower HDL-C and depression (Kim et al., 2004; Ancelin et al., 2010) and one study reported higher HDL-C than matched controls (Olusi and Fido, 1996). Similarly, contradictory findings have been published in serum triglyceride levels in depressed patients. Kinder and co-workers reported on a positive correlation between triglyceride blood levels and depression in women aged between 17 and 39 years (Kinder et al., 2004), and a positive correlation between triglyceride blood levels and the BDI score was also found in women who had received coronary angiography (Vaccarino et al., 2008). But there are also negative findings demonstrating no difference in serum TG levels between control and depressed subjects (Pjrek et al., 2007). A number of theories have been put forward to explain the contradictory findings on serum lipid disturbances in depression. Most of them emphasize the influence of the methodology used for the clinical evaluation of depression (e.g., dimensional or categorical assessment), or the impact of demographic, lifestyle and clinical variables (van Reedt Dortland et al., 2010). Furthermore, some results imply that the inconsistent findings might be due to the heterogeneity of the illness and that the

Abbreviations: ACEs, adverse childhood experiences; BDI, Beck Depression Inventory; BMI, body mass index; CPT-II, Conner's Continuous Performance Test-II; CTQ EA, Childhood Trauma Questionnaire Emotional Abuse; CTQ EN, Childhood Trauma Questionnaire Emotional Neglect; CTQ PA, Childhood Trauma Questionnaire Physical Abuse; CTQ PN, Childhood Trauma Questionnaire Physical Neglect; CTQ SA, Childhood Trauma Questionnaire Sexual Abuse; CTQ, Childhood Trauma Questionnaire; CVD, cardiovascular disease; ELS, early life stress; HC, healthy control; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDD, major depressive disorder; TC, total cholesterol; TG, triglycerides; WCST, Wisconsin Card Sorting Test.

lipid disturbances may be characteristic for only certain specific subgroups within the MDD.

So far, only a few studies considered the role of ELS in the association between depression and metabolic disturbances. McIntyre et al. (2012) found a significantly lower level of HDL-C in depressed patients who experienced childhood adversity, but there was no statistically significant difference in the overall rate of dyslipidemia and metabolic syndrome between subjects with and without childhood adversity. Ding et al. (2014) did a metabonomic analysis and reported that MDD patients had lower TC levels compared to controls, but patients with ELS had higher TC levels compared to the MDD only group. Wingenfeld et al. (2017) conducted a women-only study in a physically healthy clinical sample and found no difference in TG, cholesterol, HDL-C, LDL-C and other metabolic risk markers between MDD patients with and without sexual or physical abuse. However, one should carefully interpret these null findings, as the exclusion of obese individuals (with body mass index > 30 kg/m^2) might have led to an underrepresentation of subjects with existing obesity linked to ELS. More recently Deschênes et al. (2018) reported that ACEs are indirectly associated with diabetes via depressive symptoms and cardio-metabolic dysregulations. While Kraav et al. (2019) found decreased serum TC in depressed outpatients with a childhood history of physical violence. Importantly, most of these earlier studies – when they carried out the statistical analysis of their data – did not control for the effects of ELS, while it is well-known that the prevalence of ACEs is much higher in depressed patients compared to the general population, thus, the presence of ELS might be a confounding variable influencing the outcome of these investigations.

Psychodynamic factors, such as the loss of "good self" or "damaged self" might also have a significant impact. Individuals with ELS experience a defective or "wounded" self, and distressing feelings of shame originating from the internalization of bad or unworthy parents. According to the object relation theory, stressful life events can distort the mental representations of the self and others. This can significantly influence the individual's behavior, i.e., his or her affective states and self-care. Moreover, the damaged self can negatively impact health behavior and the adaptation to emerging somatic illnesses as well (Kohut, 1977; Ulman and Brothers, 1988; Marchini et al., 2018). Recent psychodynamic theories focus on the role of the attachment and attachment-based mentalizing capacities in the etiology and treatment of depressive disorders, and in the development of somatic disorders in individuals with ELS. Adopting a developmental approach, Luyten and Fonagy (2018) emphasized that ELS can lead to insecure attachment that impairs adaptation to stressful social situations and disrupts the regulation of the stress response. If social stress emerges, hypermentalizing and hypomentalizing can occur on the basis of the insecure attachment. These can lead to deficits of stress regulation, and to dysfunctional compensatory strategies (e.g., drug abuse, self-harm, sexual promiscuity, risk-taking, eating disorders). Due to the unhealthy behavior and the neurobiological changes as a result of ELS, MDD patients with ELS may suffer from stress-related cardiovascular and metabolic diseases more often.

In the present study, we hypothesized that serum lipid levels might be determined by ACEs in depressed patients, based on the following observations: (i) ELS can result in serum lipid alterations both in psychiatric (McIntyre et al., 2012; Misiak et al., 2015) and non-psychiatric samples (van Reedt Dortland et al., 2012; Spann et al., 2014); (ii) lipid disturbances were detected mostly in depressed patients with atypical or melancholic symptoms, or suicidal tendencies, which are more characteristic to depression with ELS (Harkness and Monroe, 2002; Matza et al., 2003; Klein et al., 2009). To investigate this hypothesis, we measured serum lipid and lipoprotein profiles in MDD patients with high and low ELS scores, and in age- and gender-matched HCs. Atherogenic indices (TC/HDL-C, LDL-C/HDL-C) and BMI was also calculated and we collected sociodemographic and clinical data on the participants' lifestyle as well. Finally, we used two well-established neuropsychological tests to measure the participant's executive functions (Wisconsin Card Sorting Test) and their attentional processes (Conners' Continuous Performance Test-II).

MATERIALS AND METHODS

Participants

Forty-two patients with MDD and 20 healthy controls (HCs) participated in this study. Patients with MDD were recruited from the Affective Disorder Unite of the Department of Psychiatry and Psychotherapy, University of Pécs, Hungary. The local Research Ethics Committee of the University of Pécs approved the study design and protocol (Ethical Approval Nr.: 2015/5626) and all participants provided written informed consent. To exclude the effects of aging, only subjects aged between 18 and 55 were involved in the study, because several studies reported an increased prevalence of dyslipidemia in the elderly population (Bechtold et al., 2006; Shanmugasundaram et al., 2010; Liu and Li, 2015).

All patients fulfilled the DSM-5 diagnostic criteria of MDD (American Psychiatric Association, 2013). Inclusion criteria of the MDD group included: (1) age 18–55 years; (2) a diagnosis of MDD in a current major depressive episode as assessed by a trained psychiatrist using the Structured Clinical Interview for DSM-5, Clinical Version, (SCID-5-CV) (First et al., 2015, 2016b) and the Structured Clinical Interview for DSM-5, Personality Disorders (SCID-5-PD) (First et al., 2016a, 2018). Exclusion criteria for the patient group were: current substance abuse or dependence (if the patient met diagnostic criteria, he or she had to be abstinent for at least 2 years), bipolar disorder, post-traumatic stress disorder, a history of any psychotic disorder, and current eating disorders. HC participants were recruited by online advertisements and via personal contacts of the researchers. The control sample was screened by a qualified psychiatrist to ascertain the absence of lifetime or family history of mental disorders. In addition, SCL-90 (Derogatis, 1977) was applied to rule out relevant subthreshold psychiatric symptoms in potentially healthy individuals. Exclusion criteria for both the patients and the controls were: liver or kidney disease, severe CVD, uncontrolled thyroid disorders, uncontrolled

diabetes mellitus, and current inflammatory illness. Subjects with known familial hyperlipidemia were not included. Subjects with neurological disorders, in addition, those with a history of head injury and with severe hearing or visual impairment, and an IQ < 85 were also excluded.

In the MDD group, treatment with antidepressant medication or psychotherapy were not exclusion criteria once the diagnosis had been established. Current psychotropic medication data were collected: 41 (97.6%) MDD subjects were taking antidepressants (20 patients were taking SSRIs, 12 mirtazapine, 2 mianserine, 2 venlafaxine, 1 duloxetine, 1 trazodone, 1 vortioxetine, 1 agomelatine), 21 (50%) low dose antipsychotics (17 quetiapine, 1 ziprasidone, 1 aripiprazole, 1 thiothixene), 5 (11.9%) mood stabilizing medications. None of the control subjects took psychotropic medication.

One MDD patient was on lipid-lowering drug (atorvastatin) treatment at the time of the study. Two patients and two control subjects kept a vegetarian diet.

Laboratory Analyses

Cubital venous blood was drawn from the participants between 7 and 8 AM in order to avoid any possible effect of circadian variations. The samples were collected following 8–12 h of fasting. Serum concentrations of TC, LDL-C, HDL-C, and TG were all measured with a Roche Modular (module P800) clinical chemistry analyzer, using enzymatic colorimetric test methods according to the manufacturer's instructions (Roche Diagnostics, Hungary).

Questionnaires

Beck Depression Inventory

The severity of actual depressive symptoms was assessed using the BDI (Beck et al., 1961; Hungarian adaptation: Petö et al., 1987; Rózsa et al., 1998). This is a 21-item self-report questionnaire rating the presence and extent of sadness, pessimism, past failure, loss of pleasure, self-dislike, self-criticism, and suicidal thoughts and wishes in the past week. The scores range from 0 to 63 points and higher scores indicate more severe depression. In this study, Cronbach's alfa values were excellent for the total BDI scores (0.95) and for the cognitive subscale scores (0.91), and good for the somatic-affective subscale (0.86).

Childhood Trauma Questionnaire-Short Form

Early life stress was surveyed with the 28-item retrospective self-report questionnaire of the Childhood Trauma Questionnaire-Short Form (CTQ) (Bernstein et al., 2003), that assesses the severity of five types of maltreatment before the age of 18 years: physical abuse (CTQ PA), emotional abuse (CTQ EA), physical neglect (CTQ PN), emotional neglect (CTQ EN), and sexual abuse (CTQ SA). Each subscale is measured with five 5-point scale items. The short form of the questionnaire is the most widely used version, which includes clinical cut-offs for significant abuse and neglect. Childhood maltreatment exposure was entered in the statistical analyses as a continuous variable with row scores, or it was coded into a two-level variable for dividing the MDD sample into low-ELS and high-ELS subgroups. Patients with MDD were assigned to the *MDD Only* subgroup if they had not experienced any types of moderate to severe childhood trauma. MDD patients were put into the *MDD + ELS* subgroup if they had at least one type of moderate to severe childhood trauma. In the present sample, the internal consistencies were excellent for the CTQ total score, and for the subscales of physical abuse, emotional abuse, sexual abuse, as well as for emotional neglect (Cronbach's alphas > 0.9). The internal consistency was acceptable for the subscale of physical neglect (Cronbach's alpha = 0.77). The Hungarian translation of the original (English) CTQ was done using the back-translation procedure (Sperber, 2004). Two senior authors (MS and BC) translated the English version to Hungarian. To ensure that the translated version is equivalent with the source version a bilingual linguist translated the early Hungarian version back to English. Errors of meaning and concept inconsistencies between the translated versions were discussed and corrected.

Sociodemographic Data on BMI and Lifestyle

A self-report questionnaire determined the various sociodemographic data, including education, lifestyle habits of regular exercise. Measurements for height and body mass were obtained using a wall-mounted stadiometer and electronic scale, respectively. BMI was calculated as body mass in kilograms divided by height in meters squared.

Neurocognitive Tests

Wisconsin Card Sorting Test

Executive functions were assessed by the computerized version of the WCST (Heaton, 1981). In the test, cards with geometric shapes (different in their number, color, and form) have to be matched according to varying sorting principles. The actual method of sorting has to be found out by the subject based on the provided feedback (correct or incorrect). Besides the number of total correct responses and non-perseverative errors, we detected the number of perseverative errors and conceptual level responses as a measure of shifting ability and conceptual ability, respectively. The WCST is a commonly used cognitive measure in clinical investigations including the studies examining cognitive changes related to depression (see e.g., Li et al., 2010; Giel et al., 2012; McGirr et al., 2012, etc.). Moreover, the WCST has been found to be a highly reliable test already decades ago (e.g., Tate et al., 1998).

Conner's Continuous Performance Test-II

Attentional processes were assessed by the CPT-II (Conners, 2000). In this task, respondents are required to press the space bar when any letter except X appears. The inter-stimulus intervals are variable (1, 2, or 4 s) with display time of 250 ms. There are six blocks, with three sub-blocks each containing 20 trials. The procedure takes 14 min to complete. Omission errors and commission errors, as well as hit reaction time and detectability (a measure of the difference between the signal [non-X] and noise [X] distributions), were assessed.

Conner's Continuous Performance Test-II is one of the most widely used, computer-administered cognitive test of attention and impulsivity. Since it is not a verbal test, and no language

adaptation is necessary thus, the reliability testing of this test was out of the scope of our study. A recent publication reported that CPT-II has a strong internal consistency, adequate test-retest reliability for commission errors and response time, and a relatively poor test-retest reliability for omission errors, and practice effects for omission and commission errors (Shaked et al., 2019). Moreover, CPT-II performances were unrelated to those in other cognitive tests, such as Stoop Color-Word test (Shaked et al., 2019). CPT-II is often used in clinical research on depression (see e.g., Godard et al., 2011; Parlar et al., 2016).

Since none of the clinical studies listed above (using either the CPT-II or the WCST) investigated the reliability of these cognitive tests, we followed the examples of the literature and assumed that both CPT-II and WCST were sufficiently reliable tests.

The Sequence of Data Collection

Research participants underwent the following study procedures. First, the clinical interviews and questionnaires were completed to assess the severity of depression and ELS. Then, a senior clinician blinded to the results of the CTQ data conducted a semi-structured interview about the stressful early life-events during childhood and adolescence. CTQ sores and the interview responses were compared, discrepancies were discussed with the participants. In the case of unresolvable discrepancies, participants were excluded from the study (n = 3). Cognitive functions were assessed separately the next day or the day after the next day. Blood samples were taken in the morning within 24 h after the initial clinical assessments.

Statistical Analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS), version 21.0. Normality was checked by normal probability plots and by the Shapiro-Wilk and the Kolmogorov-Smirnov tests. Lipid and cognitive variables that showed skewed distributions were log-transformed, and all subsequent analyses were done with these transformed data. Between-group differences in demographic, lifestyle and clinical variables were analyzed by chi-square test and by ANOVA or non-parametric tests (Mann–Whitney U and Kruskal–Wallis). Differences between the study groups in the serum lipid and lipoprotein values, as well as cognitive performances, were tested first by one-way ANOVA. If the homogeneity assumption (tested by Levene's statistic) was violated, Welch-probe was used for the group comparisons. Fisher's LSD and Games-Howell tests were applied for *post hoc* pairwise comparisons. In the next step, between-group differences in the main variables were analyzed using ANCOVA with demographic and lifestyle variables as covariates and *post hoc* comparisons were done with Bonferroni correction.

After the group comparisons, hierarchical multiple linear regression analyses were run in the entire MDD group in order to explore whether the heterogeneity of lipid and lipoprotein levels were explained rather by the severity of depression or by the severity of ELS and whether there were associations between the revealed lipid alterations and the patients' cognitive performances. Due to the relatively large number of background variables and the relatively small sample size, in the regression analyses, we selected the most relevant confounders using the forward procedure, and predictor variables of main interest were added to the models with the enter method. In the forward procedure, the predictor variables were sequentially included in the regression models depending on the strength of their correlation with the criterion variable (P to enter < 0.05). The entering procedure enters the predictor variables in the models irrespective of their significance with the criterion. In all analyses, P-values (two-tailed) below 0.05 were considered statistically significant. Effect sizes were measured by calculating Cohen's d, η^2 (for ANOVAs) as well as Cohen's f^2 (for multiple regression analyses).

RESULTS

Demographic, Lifestyle, and Clinical Data

Two-Group Comparisons: Healthy Controls Versus the Entire MDD Group

There were no significant between-group differences in age ($F_{(1,60)}$ = 0.024, P = 0.877), gender ratio ($X^2_{(1)}$ = 1.303, P = 0.254), BMI (U = 398.000, Z = −0.331, P = 0.740), and regular physical activity (U = 345.500, Z = −1.167, P = 0.243). The level of education was significantly lower (U = 190.000, Z = −3.612, $P < 0.001$), while the BDI score, as well as all CTQ scores (including total score and trauma type sub-scores) were significantly higher in MDD patients compared to the healthy subjects (BDI: Welch's $F_{(1,47.7)} = 146.324$, $P < 0.001$); CTQ Total: U = 72.500, Z = −5.238, $P < 0.001$; CTQ PN: U = 110.000, Z = −4.787, $P < 0.001$; CTQ PA: U = 186,500, Z = −3.790, $P < 0.001$; CTQ EN: $F_{(1,60)}$ = 26.407, $P < 0.001$; CTQ EA: U = 116.500, Z = −4,585, $P < 0.001$; CTQ SA: U = 230.000, Z = −3.506, $P < 0.001$) (for details see **Table 1**).

Three-Group Comparisons: Healthy Controls Versus MDD Only Versus MDD + ELS

The three groups did not differ in age ($F_{(2,59)} = 0.125$, $P = 0.883$), gender ratio ($X^2_{(2)}$ = 1.428, P = 0.490), BMI ($X^2_{(2)}$ = 0.142, P = 0.931), and physical activity ($X^2_{(2)}$ = 3.083, P = 0.214), however, a significant difference could be observed between groups in years of education ($X^2_{(2)} = 14.079$, $P = 0.001$). Pairwise comparisons showed that the level of education was significantly lower in the MDD Only and in the MDD + ELS groups compared to HC (P = 0.025, P = 0.001, respectively). As expected, CTQ total score, and the specific trauma sub-scores were significantly different between groups (CTQ Total: $X^2_{(2)} = 46.768$, $P < 0.001$; CTQ PN: $X^2_{(2)}$ = 34.441, $P < 0.001$; CTQ PA: $X^2_{(2)}$ = 30.924, $P < 0.001$; CTQ EN: $F_{(2,59)}$ = 43.020, $P < 0.001$; CTQ EA: $X^2_{(2)}$ = 37.808, $P < 0.001$; CTQ SA: $X^2_{(2)}$ = 23.897, $P < 0.001$) and *post hoc* comparisons revealed that the MDD + ELS group had significantly higher scores in all CTQ scales than the MDD Only group (CTQ Total: $P < 001$; CTQ PN: P = 0.002; CTQ PA: $P < 0.001$; CTQ EN: $P < 0.001$; CTQ EA: $P < 0.001$; CTQ SA: P = 0.002) (**Table 1**). The severity of ELS was significantly higher for physical and emotional neglect in the MDD Only group compared to HC (CTQ PN: P = 0.039; CTQ EN: P = 0.012),

TABLE 1 | Demographic, lifestyle and clinical characteristics of patients with MDD and HCs.

	HC (*n* = 20)	Entire MDD (*n* = 42)	MDD Only (*n* = 21)	MDD + ELS (*n* = 21)
Demographic and lifestyle characteristics				
Age (years)[a]	35.80 (8.53)	35.40 (9.73)	34.71 (8.17)	36.10 (11.24)
Gender (female/male)	13/7	33/9	17/4	16/5
Education (years)[b]	15.00 (5.00)	12.00 (1.00) ***	12.00 (2.00) §	12.00 (1.00) §§
Physical exercise per week (hours)	1–2	2–4	1–2	2–4
Body mass index (kg/m^2)[b]	23.39 (6.6)	23.11 (5.26)	23.12 (5.69)	23.11 (4.83)
Early life stress				
CTQ physical neglect[b]	5.00 (1.00)	9.00 (4.00) ***	7.00 (4.50) §	10.00 (5.50) §§§ $^{++}$
CTQ physical abuse[b]	5.00 (0.00)	7.00 (5.25) ***	5.00 (2.00)	10.00 (5.50) §§§ $^{+++}$
CTQ emotional neglect[a]	9.10 (3.51)	13.40 (5.42) ***	11.95 (3.56) §	18.95 (3.47) §§§ $^{+++}$
CTQ emotional abuse[b]	6.00 (2.75)	13.50 (10.25) ***	9.00 (5.50)	19.00 (5.00) §§§ $^{+++}$
CTQ sexual abuse[b]	5.00 (0.00)	5.00 (4.25) ***	5.00 (0.50)	9.00 (7.50) §§§ $^{++}$
CTQ total score[b]	29.00 (11.5)	54.50 (29.50) ***	40.00 (17.00)	69.00 (18.50) §§§ $^{+++}$
Clinical data				
BDI total score[a]	3.00 (2.13)	23.21 (10.38) ***	20.05 (10.29) §§§	26.38 (9.69) §§§
Age at the onset of MDD[b]	-	25.5 (17–32.25)	28 (18–34)	20 (16–31.5)
Number of lifetime depressive episodes[b]	-	2 (1.75–3)	2 (1–3)	2 (2–3)
Double depression (*n*)	-	2	1	1
Chronic depression (*n*)	-	5	1	4
Recurrent depression (*n*)	-	31	13	18
Lipid profile				
Total cholesterol (mmol/L)[a]	4.85 (0.91)	5.10 (1.08)	5.04 (0.88)	5.16 (1.27)
Triglycerides (mmol/L)[b]	0.89 (0.93)	1.06 (0.78)	0.92 (0.39)	1.26 (1.05) $^{+}$
HDL cholesterol (mmol/L)[a]	1.65 (0.33)	1.58 (0.37)	1.70 (0.40)	1.45 (0.28) $^{+}$
LDL cholesterol (mmol/L)[a]	2.73 (0.77)	2.95 (0.79)	2.87 (0.61)	3.03 (0.95)
LDL-C/HDL-C[b]	1.75 (0.78)	1.81 (1.05)	1.70 (0.69)	2.00 (1.33)
TC/HDL-C[b]	3.04 (1.13)	3.22 (1.29)	3.04 (1.03)	3.27 (1.78) § $^{+}$

[a]*Means and standard deviations are presented.* [b]*Medians and inter-quartile ranges are presented. Two-group comparisons: overall MDD group compared to HC: *P < 0.05, **P < 0.01, ***P < 0.001. Three-group comparisons: MDD Only compared to MDD + ELS: $^{+}$P < 0.05, $^{++}$P < 0.01, $^{+++}$P < 0.001. MDD Only or MDD + ELS compared to HC: § P < 0.05, §§ P < 0.01, §§§ P < 0.001. BDI, Beck Depression Inventory; CTQ, Childhood Trauma Questionnaire-Short Form; ELS, early life stress; HC, healthy controls; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDD, major depressive disorder; TC, total cholesterol.*

but there was no significant difference in CTQ total score, as well as in physical, emotional, and sexual abuse between these two groups (CTQ Total: $P = 0.051$; CTQ PA: $P = 0.596$; CTQ EA: $P = 0.149$; CTQ SA: $P = 0.515$). There was significant difference between the groups in BDI score (Welch's $F_{(2.29,0)} = 80.404$, $P < 0.001$) and the pairwise comparisons demonstrated that both MDD subgroups had significantly higher BDI score than the HC group ($P < 0.001$), whereas depression severity was similar in the two MDD subgroups ($P = 0.113$) (**Table 1**).

Lipid Profile

Two-Group Comparisons: Healthy Controls Versus the Entire MDD Group

No difference was found between the two groups by one-way ANOVA when we compared serum TC ($F_{(1,60)} = 0.782$, $P = 0.380$), TG ($F_{(1,60)} = 0.426$, $P = 0.516$), HDL-C ($F_{(1,60)} = 0.609$, $P = 0.438$), LDL-C ($F_{(1,60)} = 1.062$, $P = 0.307$), and the two atherogenic indices (LDL-C/HDL-C: $F_{(1,60)} = 2.052$, $P = 0.157$, TC/HDL-C: $F_{(1,60)} = 2.036$, $P = 0.159$) (**Table 1**). In order to control for the effects of demographic and lifestyle variables on lipid and lipoprotein levels, ANCOVAs were conducted with age, gender, level of education, physical exercise, and BMI as covariates, but again no significances were found (**Figure 1** and **Supplementary Table 1**).

Three-Group Comparisons: Healthy Controls Versus MDD Only Versus MDD + ELS

Results of the ANOVA omnibus tests indicated significant between-group differences in TG (Welch's $F_{(2,35.4)} = 4.367$, $P = 0.020$), HDL-C ($F_{(2,59)} = 3.293$, $P = 0.044$), and TC/HDL-C ($F_{(2,59)} = 3.434$, $P = 0.039$). *Post hoc* comparisons (Fisher's LSD and Games-Howell tests) showed that the level of HDL-C was significantly lower ($P = 0.018$), while the level of TG ($P = 0.015$) and also the ratio TC/HDL-C ($p = 0.034$) were significantly higher in the MDD + ELS than in the MDD Only group. The ratio of TC/HDL-C of the MDD + ELS group was also significantly higher when compared to the HC group ($P = 0.022$) There were no significant differences between groups in TC (Welch's $F_{(2,38.7)} = 4.367$, $P = 0.645$), LDL-C ($F_{(2,59)} = 0.733$, $P = 0.485$), and LDL-C/HDL-C ($F_{(2,59)} = 2.562$, $P = 0.086$) (**Table 1**). Cohen's *d*-values for all significant group differences ranged from 0.68 to 0.78 indicating medium-to-large effect sizes.

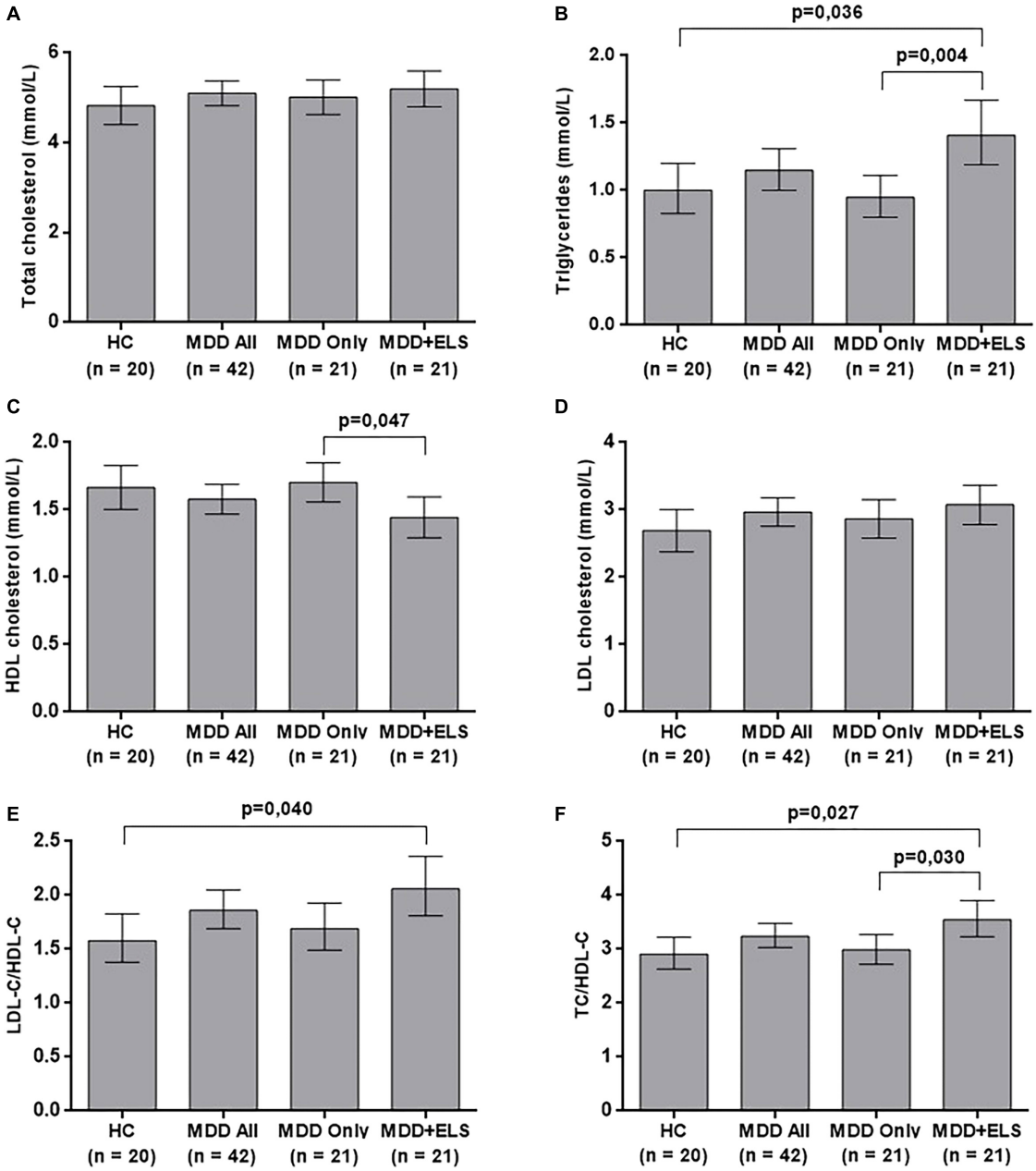

FIGURE 1 | Serum lipid and lipoprotein levels in HCs and depressed patients after the adjustment for age, gender, education, physical exercise per week, and body mass index. **(A)** total cholesterol levels; **(B)** triglyceride levels; **(C)** high-density lipoprotein cholesterol levels; **(D)** low-density lipoprotein cholesterol levels; **(E)** LDL-C/HDL-C ratio; **(F)** TC/HDL-C ratio. The bars represent the means and upper and lower 95% confidence intervals of the examined lipid profile elements. The values of triglycerides, LDL-C/HDL-C and TC/HDL-C are results of back-transformation (antilog) because of the skewed distribution of the original data. The *P*-values of significant differences are shown. ELS, early life stress; HC, healthy controls; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDD, major depressive disorder; TC, total cholesterol.

After controlling for the effects of age, gender, level of education, physical exercise and BMI by ANCOVA, between-group differences remained significant in TG ($F_{(2,54)}$ = 6.320, P = 0.003), HDL-C ($F_{(2,54)}$ = 3.409, P = 0.040), and TC/HDL-C ($F_{(2,54)}$ = 4.854, P = 0.012), and a new significant difference emerged in LDL-C/HDL-C ($F_{(2,54)}$ = 3.794, P = 0.029). As it is shown in **Figure 1**, *post hoc* Bonferroni comparisons demonstrated that HDL-C was significantly lower in MDD patients with ELS than in MDD Only patients, as well as the TG and the TC/HDL-C index, were significantly higher in the MDD + ELS group compared both to the MDD Only and to the HC groups. Moreover, higher LDL-C/HDL-C ratio was revealed in MDD + ELS patients relative to the HC. There were no significant differences between groups by ANCOVA in TC

($F_{(2,54)} = 0.742$, $P = 0.481$) and LDL-C ($F_{(2,54)} = 1.454$, $P = 0.243$) (**Figure 1**). For the significant group comparisons, Cohen's *d*-values ranged from 0.63 to 0.94 (medium-to-large effect sizes).

Multiple Linear Regression Analyses: The Effects of Depression Severity and ELS on Serum Lipid/Lipoprotein Levels

Next, we performed a series of hierarchical linear regression analyses in the entire MDD group to determine whether the heterogeneity of each lipid/lipoprotein level is explained by the severity of depression or by the amount of ELS after controlling for each other and for potentially confounding factors. Relevant confounders were selected from the demographic variables (age, gender, years of education) in Block 1, and from the lifestyle variables (BMI, physical exercise per week) in Block 2 using the forward variable selection procedure. Because we were interested in how the statistical effect of current depression severity on lipid/lipoprotein levels changes after including ELS in the models, next, in Block 3, depression severity (BDI score), and finally, in Block 4, the amount of ELS (CTQ total score) were added to the regression models using the enter method.

After running hierarchical regression analyses for each lipid and lipoprotein parameters as dependent variables, we found that in Block 3, BDI score predicted only HDL-C ($P = 0.010$) significantly. However, when the CTQ total score was also added in Block 4, the relationship between BDI and HDL-C lost its significance ($P = 0.068$) and no other significantly predictive relationship emerged between depression severity and any of the lipid profile elements (**Table 2**). However, in Block 4, the severity of ELS had a significant negative association with HDL-C level ($P = 0.040$) and a significant positive association with the serum level of TG ($P = 0.014$) and TC/HDL-C index ($P = 0.043$) (for details see **Supplementary Table 2**). Cohen's f^2-values for these significant associations ranged from 0.11 to 0.18 indicating moderate effect sizes.

The Relationship Between the Different Subtypes of ELS and Serum Lipid/Lipoprotein Levels

Within the entire MDD group, additional series of hierarchical linear regressions were calculated to determine which subtypes of childhood adversities can significantly predict the parameters of the lipid profile as dependent variables after controlling for demographic variables (Block 1), lifestyle variables (Block 2), and depression severity (BDI score; Block 3) with the forward variable selection method. In Block 4, the CTQ subscores of the different trauma types, as predictor variables of main interest, were added to the models using the 'enter' procedure.

As it is shown in **Table 3**, we found significant negative associations between physical neglect and abuse and between HDL-C. We also found significant positive associations between physical and emotional neglect and abuse, and the levels of TG. Moreover, significant positive associations were found between physical and emotional neglect and the indices of LDL-C/HDL-C and TC/HDL-C. Sexual abuse had no statistically significant relationship between any of the lipid parameters (**Table 3**; for details see **Supplementary Table 3**).

Neurocognitive Tests

Two-Group Comparisons: Healthy Controls Versus the Entire MDD Group

One-way ANOVA revealed significant group differences when we compared omission errors of the Conner's Continuous Performance Test (Welch's $F_{(1,58.5)} = 7.464$, $P = 0.008$, Cohen's $d = 0.75$). Similarly, one-way ANOVA revealed significant group differences when we compared perseverative errors of the WCST (Welch's $F_{(1,50.8)} = 5.463$, $P = 0.023$, Cohen's $d = 0.63$) (for details see **Supplementary Table 4**). After controlling by ANCOVA for age, gender, and level of education, however, these differences lost their significance (**Supplementary Table 5**).

Three-Group Comparisons: Healthy Controls Versus MDD Only Versus MDD + ELS

The ANOVA omnibus tests revealed that omission errors of the Conner's Continuous Performance Test were significantly different in the three groups (Welch's $F_{(2,36.6)} = 3.780$, $P = 0.032$, Cohen's $d = 0.64$). Further comparison with the Games-Howell *post hoc* test revealed that the CPT omission errors were significantly higher in the MDD + ELS group than in the HC ($P = 0.045$, Cohen's $d = 0.65$) (for details see **Supplementary Table 4**). However, after controlling for the effects of demographic variables, no significant between-group differences were found in the neurocognitive variables (**Supplementary Table 5**).

The Effect of Serum Lipid/Lipoprotein Levels on Neurocognitive Performances in MDD

Finally, hierarchical multiple linear regressions were calculated to predict parameters of neurocognitive tests based on lipid parameters after controlling for demographic variables (Block 1), lifestyle variables (Block 2), severity of depression (i.e., BDI score; Block 3), and severity of ELS (i.e., CTQ total score; Block 4) that were included in the regression models with the forward procedure. The lipid profile elements, as predictor variables of main interest, were added to the models using the enter method in Block 5.

Depression severity predicted commission errors in the Conner's Continuous Performance Test ($\beta = 0.289$, $P = 0.024$) and detectability ($\beta = -0.304$, $P = 0.020$), as well as conceptual level responses in the WCST ($\beta = -0{,}416$, $P = 0.006$) in Block 3 (for details see **Supplementary Tables 6**, **7**). For these significant associations between depression severity and cognitive performances, Cohen's f^2-values ranged from 0.15 to 0.20 suggesting moderate effect sizes. However, we could not find any association between the amount of ELS and any of the neurocognitive test results in Block 4. No relationship was found between lipid parameters and any of the Conner's Continuous Performance Test results (**Supplementary Table 6**). However, we could detect significant negative associations between the lipid profiles and between specific domains of the WCST. There were significant negative associations between HDL-C and WCST perseverative errors, between LDL-C/HDL-C ratio and WCST total correct responses, and also between the indices LDL-C/HDL-C and TC/HDL-C, and WCST conceptual level responses (**Table 4**, for details, see **Supplementary Table 7**).

Cohen's f^2-values for these results ranged from 0.10 to 0.16 suggesting moderate effect sizes.

DISCUSSION

The principal aim of the present study was to examine the impact of childhood adversities on serum lipid profiles in depressed patients. In our statistical analysis, we asked the question of whether depression severity or the severity of ACEs have a stronger influence determining serum lipid levels. Overall, ELS was a stronger predictor of serum lipid profiles than depression severity. Furthermore, we found that depressed patients with ELS had significantly higher serum triglyceride and lower HDL-cholesterol concentrations compared to MDD patients without ELS. The atherogenic indices, LDL-C/HDL-C, and TC/HDL-C were also higher in patients with ELS. We also found significant associations between the different trauma types and lipid profiles.

TABLE 2 | Hierarchical linear regression analyses predicting serum lipid and lipoprotein levels in the entire MDD group.

Dependent variable	Blocks	Predictors	R^2	ΔR^2	β	β'
Total cholesterol	Block 1 (forward)	Age	0.157	0.157	0.396**	0.381**
	Block 2 (forward)	Body mass index	0.304	0.147	0.384**	0.382**
	Block 3 (enter)	**Depression severity**	0.311	0.007	−0.084	−0.080
	Block 4 (enter)	**Early life stress**	0.312	0.000		−0.013
Triglycerides	Block 1 (forward)	No variable associated				
	Block 2 (forward)	Physical exercise	0.108	0.108	−0.328*	−0.396*
	Block 3 (enter)	**Depression severity**	0.145	0.038	0.198	0.031
	Block 4 (enter)	**Early life stress**	0.273	0.128		**0.400***
HDL cholesterol	Block 1 (forward)	No variable associated				
	Block 2 (forward)	No variable associated				
	Block 3 (enter)	**Depression severity**	0.156	0.156	**−0.395***	−0.280†
	Block 4 (enter)	**Early life stress**	0.243	0.088		**−0.317***
LDL cholesterol	Block 1 (forward)	Age	0.151	0.151	0.388*	0.392**
	Block 2 (forward)	Physical exercise	0.318	0.167	−0.409**	−0.453**
	Block 3 (enter)	**Depression severity**	0.327	0.009	−0.096	−0.134
	Block 4 (enter)	**Early life stress**	0.333	0.007		0.092
LDL-C/HDL-C	Block 1 (forward)	No variable associated				
	Block 2 (forward)	Physical exercise	0.129	0.129	−0.359*	−0.391*
	Block 3 (enter)	**Depression severity**	0.177	0.048	0.223	0.104
	Block 4 (enter)	**Early life stress**	0.242	0.065		0.286†
TC/HDL-C	Block 1 (forward)	No variable associated				
	Block 2 (forward)	Physical exercise	0.126	0.126	−0.355*	−0.394*
	Block 3 (enter)	**Depression severity**	0.181	0.055	0.240	0.104
	Block 4 (enter)	**Early life stress**	0.266	0.085		**0.326***

*Input variables: Block 1: demographic variables (age, gender, and years of education); Block 2: lifestyle variables (body mass index and physical exercise per week); Block 3: depression severity (BDI score); Block 4: early life stress (CTQ total score). †P < 0.1,*P < 0.05, **P < 0.01. β, standardized beta coefficient at the current step; β', the standardized beta coefficient in the final model; BDI, Beck Depression Inventory; CTQ, Childhood Trauma Questionnaire-Short Form; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDD; major depressive disorder; TC, total cholesterol. Bold values indicate the significant differences related to depression severity and ELS.*

TABLE 3 | Linear regression analyses with serum lipid and lipoprotein levels as dependent variables, and with trauma types (CTQ sub-scores) as predictors in the entire MDD group.

	Total cholesterol[a]		Triglycerides[b]		HDL cholesterol[c]		LDL cholesterol[d]		LDL-C/HDL-C[b]		TC/HDL-C[b]	
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
CTQ physical neglect	0.150	0.277	**0.351**	**0.017**	**−0.306**	**0.034**	0.179	0.182	**0.392**	**0.006**	**0.403**	**0.005**
CTQ physical abuse	−0.166	0.231	**0.320**	**0.031**	**−0.304**	**0.037**	−0.089	0.516	0.200	0.180	0.197	0.187
CTQ emotional neglect	0.176	0.198	**0.381**	**0.010**	−0.200	0.188	0.194	0.148	**0.358**	**0.014**	**0.419**	**0.004**
CTQ emotional abuse	−0.087	0.529	**0.308**	**0.041**	−0.291	0.054	0.008	0.956	0.223	0.138	0.248	0.099
CTQ sexual abuse	−0.240	0.083	0.114	0.463	0.050	0.764	−0.195	0.169	0.003	0.984	0.045	0.772

[a]Adjusted for age and body mass index. [b]Adjusted for physical exercise per week. [c]Adjusted for depression severity. [d]Adjusted for age and physical exercise per week. CTQ, Childhood Trauma Questionnaire Short Form; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDD, major depressive disorder; TC, total cholesterol. Bold values indicate the significant differences.

TABLE 4 | Linear regression analyses of serum lipid and lipoprotein levels as predictors of executive functioning (WCST scores) in the entire MDD group.

	WCST total correct responses		WCST perseverative errors[a]		WCST non-perseverative errors[b]		WCST conceptual level responses[c]	
	β	*p*	β	*p*	β	*p*	β	*p*
Total cholesterol	−0.130	0.411	−0.088	0.532	−0.038	0.794	−0.153	0.292
Triglycerides	−0.235	0.134	0.219	0.100	0.062	0.673	−0.266	0.074
HDL cholesterol	0.167	0.290	**−0.283**	**0.027**	−0.167	0.255	0.192	0.224
LDL cholesterol	−0.236	0.133	−0.068	0.629	−0.036	0.806	−0.241	0.093
LDL-C/HDL-C	**−0.306**	**0.048**	0.151	0.251	0.105	0.471	**−0.340**	**0.022**
TC/HDL-C	−0.252	0.108	0.193	0.139	0.146	0.318	**−0.309**	**0.039**

[a]Adjusted for age and education. [b]Adjusted for education. [c]Adjusted for depression severity. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDD; major depressive disorder; TC, total cholesterol; WCST, Wisconsin Card Sorting Test. Bold values indicate the significant differences.

Both physical and emotional neglect and abuse had a significant positive association with serum triglyceride levels, while physical neglect and abuse had a significant negative association with HDL-cholesterol. Finally, we could detect significant associations between depression severity and specific domains of the cognitive tests as well as between lipid profiles and certain results of the WCST. But in our study, ELS had no influence on the cognitive performance of the subjects.

A vast number of studies report that early life adversity may increase cardiovascular risk factors and the occurrence of CVD (Batten et al., 2004; Dong et al., 2004; Goodwin and Stein, 2004; Danese et al., 2009; Fuller-Thomson et al., 2010, 2012; Korkeila et al., 2010; Stein et al., 2010; Scott et al., 2011; Rich-Edwards et al., 2012; Basu et al., 2017; Murphy et al., 2017; Reid et al., 2018; Doom et al., 2019; Obi et al., 2019). These studies document that childhood adversities are associated with hypertension (Danese et al., 2009; Stein et al., 2010; Reid et al., 2018; Doom et al., 2019), higher BMI (Doom et al., 2019), ischemic heart disease (Dong et al., 2004) and myocardial infarction (Fuller-Thomson et al., 2012). Adverse childhood experience may alter serum lipid/lipoprotein profiles as adults with ELS may have elevated serum TG, LDL-cholesterol and TC as well as low HDL-cholesterol (Danese et al., 2009; Spann et al., 2014; Reid et al., 2018; Doom et al., 2019). Furthermore, a recent study reported that the different trauma types can be associated with specific changes in serum levels, i.e., physical and sexual abuse were associated with high LDL-C and low HDL-C, and childhood neglect with raised TG and low HDL-C (Li et al., 2019). The exact physiological pathways connecting ELS with CVD risk factors and CVD are yet unknown. Recently, a hypothesis has been put forward that experiencing social threat and adversity up-regulates pro-inflammatory cytokines which in turn may elicit depressive symptoms as well as metabolic syndrome and CVD (Slavich and Irwin, 2014).

Large body of evidence indicate that there is a strong association between MDD and CVD (Musselman et al., 1998; Penninx et al., 2001; Carney et al., 2002; Barth et al., 2004; Whooley, 2006; Van der Kooy et al., 2007; Goldstein et al., 2015). While the exact relationship between these two disorders remains obscure there is evidence that the presence of depressive symptoms can increase the risk of CVD (Joynt et al., 2003; Almeida et al., 2007; Vancampfort et al., 2014; Pérez-Piñar et al., 2016). Among the various CVD risk factors dyslipidemia has also been associated with depressed mood (Huang et al., 2003; Papakostas et al., 2004; van Reedt Dortland et al., 2010, 2013; Chien et al., 2013). However, the studies investigating serum lipid concentrations in MDD yielded inconsistent results. There are reports on higher (Ledochowski et al., 2003; Nakao and Yano, 2004; Moreira et al., 2017) as well as lower serum TC levels (Olusi and Fido, 1996; Maes et al., 1997; Ong et al., 2016) compared to controls, while others found no difference (Lehto et al., 2008; van Reedt Dortland et al., 2010; Enko et al., 2018). Other studies found that TG levels are increased in patients with MDD and that TG levels show a positive relationship with depression severity (Sevincok et al., 2001; Huang and Chen, 2004; Liu et al., 2016).

So far only a handful of studies examined the influence of childhood adversity on lipid profiles in depressed patients. McIntyre et al. (2012) examined a clinical population with unipolar depression and found a significantly lower level of HDL-C in patients who experienced traumatic life events during their childhood compared to those without childhood adversities. However, there was no statistically significant difference in the overall rate of dyslipidemia and/or metabolic syndrome between subjects with and without childhood adversity. Wingenfeld et al. (2017) conducted a women-only study in a physically healthy clinical sample and detected no difference in TG, cholesterol, HDL-C, LDL-C and other metabolic risk markers between MDD patients with and without sexual or physical abuse. More recently Deschênes et al. (2018) reported that ACEs are indirectly associated with diabetes via depressive symptoms and cardio-metabolic dysregulations. The most recent study found decreased TC levels in adult outpatients with MDD with a childhood history of physical violence (Kraav et al., 2019). The same study found no differences in serum levels of HDL-C and LDL-C between the groups (Kraav et al., 2019). In our present study, we could detect higher serum triglyceride and lower HDL-cholesterol levels in MDD patients who experienced childhood adversity compared to MDD patients without ELS. Furthermore, we also found that the severity of ELS had a negative association with HDL-cholesterol levels and positive associations with the serum level of TG and TC/HDL-C index. Thus, our present data support the notion that childhood adversity may influence serum lipid levels also in depressed individuals and that MDD patients with a history of childhood adversity may represent a specific sub-group within MDD. We could also detect significant associations between the different trauma types and lipid profiles. Physical neglect and

abuse had a significant negative association with HDL-cholesterol while physical and emotional neglect and abuse had a significant positive association with serum triglyceride levels. Our findings are in harmony with the recent report of Li et al. (2019), which reported that physical abuse was associated with low HDL-C, while neglect was associated with raised TG and lower HDL-C. In our present study, we could not detect any association between sexual abuse and serum lipid/lipoprotein levels. Others found that sexual abuse was associated with high LDL-C and low HDL-C (Li et al., 2019). There is, in fact, ample evidence in the literature that childhood sexual abuse can increase the incidence of CVD: a US study involving 5 900 subjects reported that childhood sexual abuse was associated with increased risk of cardiac disease (Goodwin and Stein, 2004). Another US survey involving 12 900 individuals found that specifically in men childhood sexual abuse was associated with heart attack (Fuller-Thomson et al., 2012). One should add that there are negative findings as well, e.g., a recent retrospective study involving 3 600 individuals could not reveal any consistent association between the specific type of early psychosocial adversity and CVD risk factors (Anderson et al., 2018). This study examined associations of specific types of psychosocial adversities, such as lack of maternal care, maternal overprotection, parental mental illness, household dysfunction, sexual abuse, physical and emotional abuse, and neglect in childhood with CVD risk factors including BMI, TG, low and high density lipoprotein cholesterol (Anderson et al., 2018).

A vast body of work has linked early life adversity to various types of cognitive deficits later in life (see e.g., Evans and Schamberg, 2009; Mueller et al., 2010; Pechtel and Pizzagalli, 2011; Gould et al., 2012; Chen and Baram, 2016). Cognitive impairments are also frequently present in depressed individuals (Porter et al., 2003; Marazziti et al., 2010; Ahern and Semkovska, 2017). A meta-analysis found significant cognitive deficits in executive function, memory and attention in depressed patients relative to controls (Rock et al., 2014), yet another one revealed significant correlations between depression severity and specific domains of episodic memory, executive function, and processing speed (McDermott and Ebmeier, 2009). In our present study, we could also detect significant associations between depression severity and specific domains of attention (examined with the CPT-II) and executive functions (investigated with the WCST). However, we could not find any association between ELS and cognitive performance using these two tests.

Numerous clinical and preclinical data suggest that dyslipidemia can be linked to cognitive deficits and decline (Yaffe et al., 2002; Farr et al., 2008; Gendle et al., 2008; Morley and Banks, 2010; Reynolds et al., 2010) though this issue is not without controversies (see e.g., Panza et al., 2006; Anstey et al., 2008). For example, there are reports that high TG are associated with poor memory and general cognitive decline (de Frias et al., 2007; Morley and Banks, 2010), and that high triglyceride levels inversely correlate with executive function in non-demented elderly adults (Parthasarathy et al., 2017). Furthermore, a recent study documented elevated triglyceride levels in patients with MDD, which was associated with cognitive impairments (Shao et al., 2017). In our study, we found negative associations between lipid profiles (HDL-C and LDL-C/HDL-C, TC/HDL-C ratios) and specific domains of the WCST measuring executive functions. Low levels of HDL cholesterol have been associated with poor memory (Singh-Manoux et al., 2008; Feinkohl et al., 2019), impaired executive functions (Sun et al., 2019) and cognitive decline (van Exel et al., 2002), as well as with lower gray matter volumes (Ward et al., 2010). It should be added here that higher levels of HDL-C have been associated with a decreased risk of Alzheimer's disease (Reitz et al., 2010) and that low HDL-C levels can result in cerebral amyloidosis (Reed et al., 2014).

The low sample size is a major limitation of this study. A further important limitation is that we used a retrospective self-report to asses ELS. Ideally, the long-term effects of childhood adversities should be studied in prospective longitudinal studies and using qualitative or mixed methods can also add further valuable information when studying the impact of experienced traumas (see e.g., Boeije et al., 2013; Esposito et al., 2019), especially because self-reports can be biased. For example, social desirability can be an important potential bias when reporting past traumatic events especially in health-related research (see e.g., Adams et al., 2005; van de Mortel, 2008; Caputo, 2017 on this topic). Another limitation of our study design is that it does not allow to derive causal relations, but only associations. To compensate these limitations we did our best to carefully select the participants and match them in age, gender, lifestyle habits, and clinical data. Notably, only a few studies (Ding et al., 2014; Wingenfeld et al., 2017) included a control group in their studies, besides the MDD patients with or without ELS. We also carefully analyzed the influence of the various ACE subtypes. Finally, we also assessed the cognitive performance of our subjects and none of the earlier studies did such measurements.

Our present findings, together with the results available in the literature, have important clinical implications regarding the psychological interventions in case of depressed patients with ELS. Several studies demonstrated that depressed adults who experienced ELS react less well to conventional treatments than those who were not exposed to stressful life events during childhood (reviewed by Targum and Nemeroff, 2019). There is some evidence that MDD with ELS reacts much better to cognitive behavioral therapy (Nemeroff et al., 2003; Niciu et al., 2015) or interpersonal therapy (Zobel et al., 2011) than to pharmacotherapy. Psychodynamic therapies, as well as mentalizing-based therapy, can also be beneficial for MDD patients with ELS (Alessi and Kahn, 2017; Luyten and Fonagy, 2018). Our data emphasize the importance of the screening for ELS in the clinical MDD population. In case of early emotional abuse and emotional and physical neglect, we should consider psychotherapeutic interventions. Relying on relational cooperation, psychodynamic psychotherapy interventions can be especially helpful for patients with ELS, as they can establish an atmosphere of acceptance and safety, factors that are extremely relevant in early traumatized individuals. The holding environment and containment, created in this way, can provide a basis for the therapy of mood symptoms, and it may also reduce the risks for somatic complications. In addition, mentalizing based therapy can support early traumatized patients with an insecure attachment to regulate their negative affective states, and

reduce stress, instead of using unhealthy methods to cope with stressful situations.

In summary, our present data provide further evidence that childhood adversity may increase the risk of CVD. We found that depressed patients with ELS had higher serum triglyceride and lower HDL-cholesterol concentrations compared to patients without ELS. The severity of childhood adversity and the different trauma types showed specific associations with the lipid profiles, but we could not find any association between the severity of ELS and cognitive performance. Further research is needed to clarify the exact intermediary factors in order to gain a better understanding on the physiological mechanisms linking childhood adversities to cardio-metabolic disease, including the exploration of the difference as well as common pathways for specific maltreatment. Importantly, these issues should preferably be investigated in longitudinal studies as the retrospective self-reported measures might be biased. Finally, our present findings highlight the importance of controlling ELS, especially when a psychiatric sample is studied and treated.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the **Supplementary Files**.

ETHICS STATEMENT

The local Research Ethics Committee of the University of Pécs approved the study design and protocol (Ethical Approval Nr.: 2015/5626) and all participants provided written informed consent.

AUTHOR CONTRIBUTIONS

ÁP, BC, and MS conceived the study, designed the experiments, and wrote the manuscript. NN carried out the psychological and neurocognitive tests with the subjects, analyzed the data, prepared the tables and the figure, and wrote the manuscript. RH helped with the statistical analysis. MS selected the patients and made the diagnosis. TT and AM provided supervision and had helpful comments on the interpretation of the data. All authors contributed to the writing of the manuscript and/or revising it critically for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2019.01798/full#supplementary-material

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BRIEF RESEARCH REPORT
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Examining the Relationship Between Executive Functions and Mentalizing Abilities of Patients With Borderline Personality Disorder

*Nándor Németh[1], Ágnes Péterfalvi[2], Boldizsár Czéh[1,2], Tamás Tényi[3] and Maria Simon[1,3]**

[1] Neurobiology of Stress Research Group, János Szentágothai Research Centre, University of Pécs, Pécs, Hungary, [2] Department of Laboratory Medicine, Medical School, University of Pécs, Pécs, Hungary, [3] Department of Psychiatry and Psychotherapy, Medical School, University of Pécs, Pécs, Hungary

Patients with borderline personality disorder (BPD) experience interpersonal dysfunctions; therefore, it is important to understand their social functioning and the confounding factors. We aimed to investigate the mentalizing abilities and executive functioning (EF) of BPD patients and healthy subjects and to determine the relative importance of BPD diagnosis and EF in predicting mentalizing abilities while controlling for general IQ and comorbid symptom severity. Self-oriented mentalizing (operationalized as emotional self-awareness/alexithymia), other-oriented mentalizing [defined as theory of mind (ToM)], and several EF domains were examined in 18 patients with BPD and 18 healthy individuals. Decoding and reasoning subprocesses of ToM were assessed by standard tasks (Reading the Mind in the Eyes Test and Faux Pas Test, respectively). Relative to controls, BPD patients exhibited significant impairments in emotional self-awareness and ToM reasoning; however, their ToM decoding did not differ. Multivariate regression analyses revealed that comorbid psychiatric symptoms were negative predictors of alexithymia and ToM decoding. Remarkably, the diagnosis of BPD was a positive predictor of ToM decoding but negatively influenced reasoning. Moreover, EF had no impact on alexithymia, while better IQ, and EF predicted superior ToM reasoning. Despite the small sample size, our results provide evidence that there is a dissociation between mental state decoding and reasoning in BPD. Comorbid psychiatric symptoms could be considered as significant negative confounds of self-awareness and ToM decoding in BPD patients. Conversely, the impairment of ToM reasoning was closely related to the diagnosis of BPD itself but not to the severity of the psychopathology.

Keywords: borderline personality disorder, mentalization, alexithymia, theory of mind, Reading the Mind in the Eyes Test, Faux Pas Test, executive functioning, symptom severity

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***Correspondence:**
Maria Simon
simon.maria@pte.hu

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INTRODUCTION

Borderline personality disorder (BPD) is a psychiatric condition characterized by three symptom clusters including affective dysregulation, impulsivity, and disturbed relatedness (Sanislow et al., 2002). According to the mentalization-based model of BPD (Sharp and Kalpakci, 2015; Fonagy and Luyten, 2016), these features of BPD can be viewed as a consequence of impairments

in the capacity to mentalize, i.e., to understand behavior in terms of underlying mental states. According to this theory, mentalization is defined as a multidimensional construct involving several dimensions and abilities. One of these dimensions relates to the objects of mentalizing: it can be directed either toward the mental states of the self or toward the mental states of others.

Impairment of self-oriented mentalizing can be manifested as low levels of emotional self-awareness or alexithymia (Choi-Kain and Gunderson, 2008). Alexithymia is a clinical condition characterized by an inability to identify and describe one's own affective experiences (Taylor et al., 1997). Studies have found that borderline patients are more alexithymic than healthy controls (for a meta-analysis, see Derks et al., 2017) and reported relationships between BPD individuals' alexithymic traits and the severity of their symptoms (e.g., Gaher et al., 2013; McMain et al., 2013). However, to date, no attention has been paid to the potential neurocognitive underpinnings of alexithymia in BPD.

Other-oriented mentalizing can be operationalized as theory of mind (ToM) (Choi-Kain and Gunderson, 2008), a social cognitive function by which we can attribute mental states, such as beliefs, intentions, and emotions, to others (Baron-Cohen et al., 1985). ToM is a multidimensional construct and consists of several subprocesses (Tager-Flusberg and Sullivan, 2000; Sabbagh, 2004). Mental state decoding is the social–perceptual aspect of ToM, which involves the ability to detect and discriminate others' mental states based on their observable social behavior. Mental state reasoning implies the social–cognitive subcomponent, involving causal inferences and predictions about others' mental states based on additional information sources including context and general social knowledge.

Findings on ToM performance in BPD indicate that the decoding and reasoning subprocesses of ToM may be unequally affected by the disorder. Several studies have found that BPD patients exhibited intact or even enhanced ability to decode others' mental states based on facial expressions (Fertuck et al., 2009; Frick et al., 2012; Zabihzadeh et al., 2017). By contrast, other studies have shown that borderline patients perform worse than healthy controls on ToM reasoning tasks (Harari et al., 2010; Brüne et al., 2016), but the severity of their deficit is task dependent (Petersen et al., 2016). It has been suggested that BPD patients' ToM impairment becomes apparent in more complex tasks that require contextual processing and the integration of multiple mental state perspectives (Baez et al., 2015; Petersen et al., 2016). This raises the possibility that the difficulties of BPD patients in ToM reasoning are not due to deficits in their basic ToM abilities but rather to deficits in neurocognitive skills, mainly in executive functioning.

Executive functioning (EF) refers to capabilities that enable flexible and goal-directed responses in novel or complex situations. Through the higher-order monitoring and regulation of cognitive subprocesses, EF plays an important role in the operation of many cognitive functions (Chan et al., 2008). The role of EF in mentalizing abilities is a widely investigated topic in both clinical and non-clinical samples. Regarding emotional awareness, it has been hypothesized that the cognitive systems that are responsible for the higher-level elaboration of emotional experiences are not specialized for emotional processing but rather implement domain-general executive functions (LeDoux, 2000; Lane and Garfield, 2005). This notion implies that executive dysfunction may cause disturbances in emotional self-awareness. Supporting this idea, several studies have found a relationship between poor performance on EF tasks and alexithymic symptoms (e.g., Henry et al., 2006; Santorelli and Ready, 2015).

Concerning the EF–ToM relationship, it has been suggested that these two abilities are implemented by two separate but interacting cognitive systems (Stone and Gerrans, 2006; Aboulafia-Brakha et al., 2011; Wade et al., 2018). According to this view, there are cognitive mechanisms specifically involved in the representation of mental states, but domain-general executive processes are required to efficiently manage and properly apply those representations in complex circumstances. In line with this assumption, many behavioral studies have demonstrated that performance on EF tests shows association with ToM performance, mainly in the case of those complex ToM tasks that have high cognitive load and contextual demands (Aboulafia-Brakha et al., 2011; Ahmed and Stephen Miller, 2011). These results suggest that EF is more strongly related to the reasoning aspect of ToM than to the decoding component.

There is a lack of research on the relationship between mentalizing abilities and EF in BPD. This limitation is particularly striking in studies that have demonstrated structural and functional abnormalities in frontal executive brain areas and impaired behavioral performance on executive tasks in borderline patients (Krause-Utz et al., 2014; McClure et al., 2016). Given this gap in the literature, the present study addressed two objectives. The first aim was to analyze simultaneously the mentalizing and executive profiles of BPD patients by comparing their performance to healthy individuals on tasks assessing different subdomains of mentalization and EF. Our second aim was to perform multivariate analyses to determine the relative importance of BPD diagnosis and EF in predicting alexithymia, as well as ToM performance while considering the potential effects of psychiatric symptom severity and general intelligence.

METHODS

Participants

BPD patients ($N = 18$) were recruited from the Affective Disorder Unit of the Department of Psychiatry and Psychotherapy, University of Pécs. All patients fulfilled the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) diagnostic criteria for BPD (American Psychiatric Association [APA], 2013). Exclusion criteria for the patient group were any other personality disorder, psychotic disorders, bipolar disorder, posttraumatic stress disorder, current substance use disorder, a history of head injury, neurological diseases, and intellectual disability. Healthy controls (HC, $N = 18$) were recruited through online advertisements. Exclusion criteria for controls included any mental disorder, a history of substance abuse, a history of neurological disorders, and head injury with loss of consciousness for more than 30 min, an IQ < 85, and any learning difficulties.

All participants lived in the urban and suburban area of Pécs, were Caucasian, and native Hungarian speakers.

The diagnoses were established with structured clinical interviews (SCID-5-CV: First et al., 2016; SCID-5-PD: First et al., 2018). The severity of psychiatric symptoms was assessed with the Symptom Check List-90-Revised (SCL-90-R) questionnaire (Derogatis, 1977; Unoka et al., 2004), and the overall level of intelligence (IQ) was estimated with a four-subtest version of the Wechsler Adult Intelligence Scale-Revised (Kaufman et al., 1991). At the time of the investigations, 17 of the 18 patients were on psychotropic medication. Healthy controls were matched pairwise to the patients for sex, age (±4 years), education (±2 years), and IQ (±5 points). None of the healthy individuals took psychotropic medication. The clinical and demographic data are presented in **Table 1**.

All subjects gave written informed consent, and the study was approved by the Research Ethics Committee of the Faculty of Humanities, University of Pécs (Ethical Approval No.: 2015/1).

Instruments

Executive Function Tasks

Four subdomains of executive functioning (EF) were measured: (1) mental set shifting [with Wisconsin Card Sorting Test (WCST); Berg, 1948]; (2) working memory updating [with Listening Span Task (LST); Daneman and Blennerhassett, 1984; Janacsek et al., 2009]; (3) prepotent response inhibition [with Eriksen Flanker Task (FT); Eriksen and Schultz, 1979]; and (4) long-term memory access [with the Letter Fluency Task (LFT); see Strauss et al., 2006; Tánczos et al., 2014]. The WCST and the FT were computerized tasks taken from the Psychology Experiment Building Language (PEBL) test battery (Mueller and Piper, 2014). The EF variables of interest were the number of perseverative errors on the WCST, the number of words remembered in the LST, the interference time on the FT, and the number of words generated in the LFT. To get a global measure of executive functioning, we calculated an average *z* score from these four EF variables, which was converted into a *t* score (= composite EF score).

Mentalizing Tests

The level of emotional self-awareness/alexithymia was surveyed using the total scores of the 20-item self-report Toronto Alexithymia Scale (TAS-20; Bagby et al., 1994; Cserjési et al., 2007).

ToM capacities were examined with two standard ToM tasks. To measure ToM decoding ability, we used the Reading the Mind in the Eyes Test (RMET, Baron-Cohen et al., 2001; Ivády et al., 2007). This task is composed of 36 black-and-white photographs depicting the eye region. For each photograph, four mental state words were displayed, and the participants' task was to decide which one best described what the person in the picture was feeling or thinking. As the RMET requires recognition of others' mental states based on static and socially decontextualized perceptual stimuli, it does not necessitate contextual processing and complex inferences about mental states. Thus, the RMET is regarded as a prototypical task to measure the social–perceptual, decoding aspect of ToM (Sabbagh, 2004; Bora et al., 2006; Richman and Unoka, 2015).

TABLE 1 | Demographic and clinical characteristics of the study samples.

	BPD (*n* = 18)		HC (*n* = 18)		*t*-value	*P*-value
Demographics						
Gender ratio (female/male)	17/1		17/1			
Age in years (mean ± SD)	34.72 ± 8.02		34.11 ± 9.39		0.210	0.835
Education level in years (mean ± SD)	12.78 ± 3.30		12.89 ± 2.78		−0.240	0.812
IQ estimate (mean ± SD)	109.79 ± 8.22		112.99 ± 8.60		−1.139	0.262
Psychiatric symptom severity						
SCL-90-R GSI (mean ± SD)	2.06 ± 0.66		0.40 ± 0.28		9.769	**<0.001**
SCL-90-R PST (mean ± SD)	66.94 ± 12.24		23.22 ± 12.42		10.639	**<0.001**
SCL-90-R PSDI (mean ± SD)	2.71 ± 0.47		1.48 ± 0.54		7.210	**<0.001**
	n	**%**	***n***	**%**	**Chi square**	***P*-value**
Current comorbid disorders						
Depressive disorders	10	55.5	0	0	13.85	**<0.001**
Anxiety disorders	6	33.3	0	0	7.2	**<0.01**
Substance use disorders	5	27.7	0	0	5.81	**0.016**
Eating disorders	1	5.5	0	0	1.014	**0.31**
Medications						
Antidepressants	11	61.1				
Benzodiazepines	13	72.2				
Mood stabilizers	9	50				
Antipsychotics	16	88.8				

Statistically significant P-values are written in bold. BPD, borderline personality disorder; HC, healthy controls; IQ, intelligence quotient; SCL-90-R, Symptom Check List-90-Revised; GSI, Global Severity Index; PST, Positive Symptom Total; PSDI, Positive Symptom Distress Index; SD, standard deviation.

ToM reasoning was assessed with the Faux Pas Test (FPT, Stone et al., 1998; Gál et al., 2011, 2014). This task consists of 20 short stories about different interpersonal situations that may or may not contain a social faux pas. After each story, participants were asked whether any of the story characters said something awkward. If participants said yes, further questions were raised regarding the characters' cognitive and affective mental states. As a story-based verbal task, the FPT does not involve perceptual processing and requires causal inferences about the characters' mental states on the basis of information provided by the contextual scenes and general social knowledge. Based on these features, the FPT is regarded as an appropriate task to investigate the social–cognitive, reasoning aspect of ToM (Wang et al., 2008; Thoma et al., 2013; Faiśca et al., 2016). (Detailed information about tests used in the study is reported in the **Supplementary Material**).

Statistical Analysis

Between-group differences in demographic, clinical, neuropsychological, alexithymia, and ToM variables were analyzed using independent-samples *t* tests. For EF and mentalizing measures, we calculated Cohen's *d* effect sizes. After the between-group comparisons, assumptions were tested, and multiple linear regression analyses were run in the whole sample. In the regression models, the total scores of TAS-20, RMET, and FPT were separately taken as dependent variables. BPD diagnosis (coded as a dummy variable: 0 = absence of the diagnosis, 1 = presence of diagnosis), SCL-90-R Global Severity Index (GSI), estimated IQ, as well as the composite EF scores were used as predictors in all models. To estimate the effect sizes of the predictors, Cohen's f^2 values were calculated. *P*-values (two-tailed) ≤ 0.05 were considered statistically significant.

RESULTS

Between-Group Comparisons

The demographic and clinical features of BPD and HC groups are shown in **Table 1**. The groups were matched in terms of gender, age, education level, and estimated IQ. On the SCL-90-R questionnaire, the BPD group had significantly higher depression, anxiety, and global severity scores than the controls.

Group means and results of between-group comparisons for EF and mentalizing performances are presented in **Table 2**. There were no significant between-group differences in any EF domains. (We found a medium effect size for the composite EF and Inhibition scores, with a trend level significance of between-group difference for the latter one).

Mentalizing Abilities

The BPD group had a significantly higher alexithymia score on the TAS-20 relative to the HC group ($P < 0.001$, Cohen's $d = 1.31$). In our sample, ToM decoding (RMET) performances in the two groups did not significantly differ. However, the BDP group showed a significant impairment in ToM reasoning ($P = 0.026$, Cohen's $d = -0.78$), as demonstrated by their lower mental state inference score on the FPT.

Regression Analyses in the Whole Sample

Alexithymia

The multiple regression model predicting alexithymia was significant, explaining 56.9% of the variance in the TAS-20 scores. The diagnosis of BPD, the estimated IQ, and the composite EF score were non-significant predictors with small-to-medium effect sizes. General psychiatric symptom severity was the only significant predictor in the model ($P = 0.002$, Cohen's $f^2 = 0.36$) (**Table 3**).

ToM Decoding

The multiple regression model predicting ToM decoding accuracy was significant, accounting for 29.2% of the variance in the RMET scores. In this model, BPD diagnosis predicted significantly better performance on the RMET ($P = 0.05$, Cohen's $f^2 = 0.14$). However, greater psychiatric symptom severity was related to significantly worse performance ($P = 0.021$; Cohen's $f^2 = -0.19$). The cognitive variables and IQ were non-significant predictors with small effects (**Table 3**).

ToM Reasoning

The multiple regression model predicting ToM reasoning ability was significant, with 49.8% of the variance in the FPT scores accounted for by the predictors. BPD diagnosis was a significant negative predictor of FPT performance ($P = 0.032$, Cohen's $f^2 = -0.16$). Higher estimated IQ and composite EF scores predicted significantly better performance on the FP ($P = 0.015$, Cohen's $f^2 = 0.21$, and $P = 0.007$, $f^2 = 0.27$, respectively). Only the general symptom severity was a non-significant predictor in this model (**Table 3**).

DISCUSSION

This is the first study to examine the relationship between EF, alexithymia, and ToM in BPD while simultaneously considering the confounding effects of psychiatric symptom severity and general IQ. Our results strengthen the notion that BPD patients' mentalizing subdomains are dissociated: their self-awareness and ToM reasoning were impaired, while their ToM decoding was comparable with those of healthy controls. In a series of multiple regression models, we tested the relative predictive value of EF, IQ, the comorbid clinical symptoms, and the diagnosis of BPD on mentalizing capacities. Comorbid psychiatric symptoms had significantly negative relative importance while predicting self-awareness/alexithymia and ToM decoding. However, the diagnosis of BPD was proved to be a significant negative predictor of ToM reasoning but a positive predictor of decoding. EF and IQ positively influenced BPD patients' ToM reasoning.

The Executive and Mentalizing Profile of BPD

For assessing EF, we adopted theories about the fractionation of EF into different subcomponents (Miyake et al., 2000; Fisk and Sharp, 2004). There were no statistically significant between-group differences in any EF measures. However, BPD patients

TABLE 2 | Executive functions and mentalizing abilities in patients with borderline personality disorder (BPD) and healthy control (HC).

	BPD (n = 18)		HC (n = 18)		t-value	P-value	Cohen's d
	Mean	SD	Mean	SD			
Executive functions							
Shifting (WCST perseverative errors)[a]	10.61	5.20	8.78	4.91	1.088	0.284	0.36
Updating (LST working memory span)	3.37	0.68	3.65	0.89	−1.046	0.303	−0.35
Inhibition (FT interference time)[a]	43.85	23.74	29.17	25.17	1.800	0.081	0.60
Access (LFT total words)	50.39	15.21	51.78	16.44	−0.263	0.794	−0.09
Composite executive function score	46.62	6.76	50.00	5.65	−1.629	0.113	−0.54
Mentalizing							
Alexithymia (TAS-20 total score)[a]	59.00	12.78	43.67	10.48	3.936	<**0.001***	**1.31**
ToM decoding (RMET total score)	24.67	4.17	25.56	2.77	−0.753	0.457	−0.25
ToM reasoning (FPT total score)	27.78	5.94	31.89	4.55	−2.332	**0.026**	**−0.78**

*Group means and between-group comparisons. BPD, borderline personality disorder; HC, healthy controls; WCST, Wisconsin Card Sorting Test; LST, Listening Span Task; FT, Flanker Task; LFT, Letter Fluency Task; TAS-20, Toronto Alexithymia Scale-20 items; RMET, Reading the Mind in the Eyes Test; FPT; Faux Pas Test; SD, standard deviation.[a]Higher scores indicate worse functioning. Statistically significant results are presented in bold. *Significant after Bonferroni correction. Cohen's d values of 0.2, 0.5, and 0.8 represent small, medium, and large effect sizes, respectively.*

TABLE 3 | Multiple regression models for mentalizing abilities.

Variables	B	Std. Error	Beta	t-value	P-value	Cohen's f^2
Alexithymia[a]						
Constant	73.288	26.942		2.720	0.011	
BPD diagnosis	−5.479	6.694	−0.200	−0.818	0.419	−0.02
Symptom severity	12.797	3.805	0.904	3.363	**0.002**	**0.36**
IQ estimate	−0.308	0.233	−0.187	−1.322	0.196	−0.06
Executive functioning	4.271	3.098	0.196	1.379	0.178	0.06
Theory of Mind decoding[b]						
Constant	25.170	8.749		2.877	0.007	
BPD diagnosis	4.440	2.174	0.640	2.043	**0.050**	**0.14**
Symptom severity	−3.015	1.236	−0.841	−2.440	**0.021**	**−0.19**
IQ estimate	0.014	0.076	0.034	0.187	0.853	0.00
Executive functioning	0.805	1.006	0.146	0.800	0.430	0.02
Theory of Mind reasoning[c]						
Constant	1.224	11.743		0.104	0.918	
BPD diagnosis	−6.559	2.918	−0.592	−2.248	**0.032**	**−0.16**
Symptom severity	2.767	1.658	0.484	1.669	0.105	0.09
IQ estimate	0.262	0.101	0.394	2.577	**0.015**	**0.21**
Executive functioning	3.895	1.350	0.442	2.885	**0.007**	**0.27**

Predictors of mentalizing abilities in the whole sample (n = 36). Cohen's f^2 values of 0.02, 0.15, and 0.35 represent small, medium and large effect sizes, respectively. Statistically significant results are presented in bold. BPD, borderline personality disorder; IQ, intelligence quotient. [a]$F(4,31) = 10.24$, $P < 0.001$. [b]$F(4,31) = 3.19$, $P < 0.026$. [c]$F(4,31) = 7.70$, $P < 0.001$.

performed worse in the inhibition component of EF at a trend level significance ($P = 0.081$, with a medium effect size: Cohen's $d = 0.6$). This trend-level between-group difference is in harmony with prior studies suggesting that deficits in response inhibition may be of central importance in BPD (Posner et al., 2002; Rentrop et al., 2008; Ruocco et al., 2012; van Dijk et al., 2014; Unoka and Richman, 2016). We can presume that the lack of significance was due to the low statistical power resulting from our small sample size.

Similarly to previous studies (for a review, see Derks et al., 2017), we found that BPD patients were significantly impaired relative to controls in their ability to mentalize (recognize and describe) their emotional states. Other-oriented mentalizing was operationalized in our study as ToM. The decoding and reasoning subcomponents of ToM were examined by prototypical tasks, the Reading the Mind in the Eyes Test, and the Faux Pas Test, respectively. Our results indicated that BPD patients' ability to decode others' mental states was preserved. By contrast, patients with BPD were impaired in their ability to reason about the mental states of others, evidenced by a large between-group difference in the number of correct mental state attributions on the Faux Pas Test. These findings replicated the results of several preceding studies and our recent meta-analysis that found similar performance on the RMET but substantially

poorer performance on the Faux Pas Test in borderline patients compared to healthy controls (Baez et al., 2015; Petersen et al., 2016; Zabihzadeh et al., 2017; Németh et al., 2018). Our results endorse findings suggesting that the mentalizing profile in BPD is characterized by a dissociation between the decoding and the reasoning subprocesses of ToM.

Factors Influencing Mentalizing Abilities

In our multiple regression model, neither general IQ nor global executive functioning was a significant predictor of alexithymia. Interestingly, not the diagnosis of BPD, but greater severity of comorbid psychiatric symptoms has been proven to be a relative predictor of a higher TAS-20 score. These findings are in line with prior studies (e.g., Loas et al., 2012; Pluta et al., 2018) demonstrating that borderline individuals are more alexithymic than healthy controls; however, this difference can mainly be explained by their comorbid clinical symptoms, especially by depression and anxiety. Although previous research has demonstrated a relationship between executive functioning and alexithymia in various clinical and non-clinical samples (Henry et al., 2006; Bogdanova et al., 2010; Koven and Thomas, 2010; Santorelli and Ready, 2015), our results suggest no relationship between these two abilities in BPD. Nevertheless, our study is the first that investigated this relationship in BPD; thus, further research with an extended number of cases is needed on this topic.

Remarkably, the multiple regression analysis predicting ToM decoding ability demonstrated opposing effects of BPD diagnosis and the severity of psychiatric symptoms. While BPD diagnosis predicted better performance on RMET, greater severity of coexisting psychiatric symptoms was associated with worse response accuracy. Previous studies using the RMET in borderline patients yielded inconsistent results, reporting reduced accuracy (Unoka et al., 2015; Van Heel et al., 2019), enhanced accuracy (Fertuck et al., 2009; Zabihzadeh et al., 2017), or no significant difference (Schilling et al., 2012; Baez et al., 2015) compared to healthy controls. Our findings suggest that the inconsistency of prior studies may be at least partly due to the confounding effect of the severity of psychiatric symptoms.

We found that BPD diagnosis was independently related to worse reasoning performance on the FPT, while psychiatric symptom severity was not a significant predictor in the model. However, both higher general IQ and better global EF were independently related to higher FPT scores. Contrary to our RMET results, here, we found that better EF was related to improved FPT performance. These findings suggest that these two ToM tasks may rely on different mechanisms. With its decontextualized stimuli, the RMET does not require contextual processing and complex reasoning processes. The FPT is a verbal task and requires causal inferences about mental states based on short stories in real-life social contexts. In the FPT, adequate mental state attribution depends not only on the ability to extract relevant information from the context but also on the ability to integrate representations of the characters' mental states. Moreover, FPT also involves linguistic processing and other non-social cognitive skills and imposes additional cognitive load relative to the RMET. Our results suggest that this additional load uses up mainly executive function resources. These findings are in line with previous studies that examined the relationship between EF and ToM using RMET and FPT (e.g., Ahmed and Stephen Miller, 2011; Thoma et al., 2013; Baez et al., 2015; Torralva et al., 2015) and support the notion that the higher-order, reasoning aspect of ToM is more closely linked to domain-general cognitive abilities and prefrontal functioning than the lower-order, decoding component (Tager-Flusberg and Sullivan, 2000).

BPD diagnosis was also independently related to FPT performance in the multiple regression analysis. This negative effect of BPD remained significant in the model even after adjusting for general IQ, global EF, and psychiatric symptom severity. This suggests that mental state reasoning deficit might be a stable characteristic of the BPD. To date, only one study has examined the relationship between EF and ToM in BPD (Baez et al., 2015). Using similar ToM tasks, this research group found deficits both in EF and mental state reasoning in borderline patients. In their multivariate analysis, EF was significantly related to ToM reasoning performance, but BPD diagnosis was not a significant predictor of this ability, suggesting that mental state reasoning deficit is not a core feature of BPD, but is rather a consequence of executive dysfunction. Nevertheless, the small sample size is a major limitation for both studies; the contradictory relationship between EF and ToM in BPD deserves further examination.

Limitations

The main limitation of our study was the low statistical power due to the small sample size. Thus, all of our findings must be treated as preliminary and should be replicated in larger samples. We should very carefully interpret our results especially those with EF. Executive dysfunction was suggested to play an important role in the pathomechanisms of BPD (Fertuck et al., 2006; Sebastian et al., 2014). A recent meta-analysis on neuropsychological functioning in BPD (Unoka and Richman, 2016) found a moderate effect size (Cohen's d = -0.54) for EF impairment, which is the same as that on our composite EF scores. We can assume that our non-significant result in the between-group comparison of EF scores (P = 0.113) is largely due to the low number of cases.

Moreover, no clinical comparison group was included in the study; therefore, we did not investigate whether the detected mentalizing profile and its confounders are specific for BPD. BPD patients were recruited from the acute clinical setting. We did not examine demographic variables such as marital status and employment and did not follow-up on the sample to test how mentalizing abilities, cognitive functions, and comorbid clinical symptoms correlated with the demographic variables related to the functional outcome. Due to the high variability of comorbid psychiatric disorders and the psychotropic medications taken by BPD patients, it was not possible to form homogeneous subgroups to test the effect of these factors. Although a large proportion of our patients were on psychotropic medication (mainly on low-dose atypical antipsychotics), the impact of psychoactive drugs was not examined here. Finally, we only considered the severity of

comorbid psychiatric symptoms measured by SCL-90; no other clinical questionnaires were applied.

CONCLUSION

Acknowledging the limitations, the present study provides some important clues for therapy and future research on mentalizing abilities in patients with BPD. Our study presents further evidence that there is a dissociation between ToM decoding and reasoning abilities in BPD. Our results fit well to the theory of Fonagy and Bateman (2008): BPD patients who grow up in a non-reflecting, non-validating, and often abusing family environment develop an increased emotional vigilance to social stimuli, especially to those with negative emotional content. Nevertheless, BPD patients' ToM abilities are just partially developed, since their reflexive awareness is low, and their mental state reasoning abilities are significantly impaired.

Based on our limited results, clinicians should carefully monitor BPD patients' comorbid psychiatric symptoms and consider that comorbid symptoms can negatively impact the patients' self-awareness and mental state decoding abilities. Conversely, impairment in mental state reasoning appears to be a core feature of BPD, but better IQ and EF can positively influence this deficit. However, regarding the low number of cases in our present study, further research is necessary to test our data in a larger sample.

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 Research Ethics Committee of the Faculty of Humanities, University of Pécs. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NN and TT conceived the study and designed the experiments. NN collected and analyzed the data and drafted the manuscript. ÁP helped with the interpretation of data and writing of the manuscript. MS selected the patients, made the diagnosis, and revised the manuscript for publication. MS and BC raised funding and provided supervision and had helpful comments on the interpretation of the data. All authors contributed to the writing of the manuscript and/or revising it critically for important intellectual content. All authors approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2020.01583/full#supplementary-material

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