Neuroscience and Biobehavioral Reviews 94 (2018) 166–178

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Biomarker correlates of psychotherapy outcomes in borderline personality disorder: A systematic review

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ARTICLE INFO

Keywords:
Systematic review
Borderline personality disorder
Biomarkers
Treatment response
Treatment outcomes
Psychotherapy
Neuroimaging
Genetic
Neuroendocrine
Behavior therapy
Psychological treatment

ABSTRACT

Studies of neurobiological mechanisms in borderline personality disorder (BPD) have increased our understanding of the pathophysiology of its development and course. Less is known about how psychotherapy may influence these neurobiological factors, and also whether biomarkers may predict psychotherapy outcomes. We conducted a systematic review using PRISMA guidelines. Fourteen studies providing data from 467 participants diagnosed with BPD met inclusion criteria to: (a) investigate biomarkers predicting response to psychotherapy for BPD; or (b) examine neurobiological factors altered by psychotherapy. Neuroimaging studies (n = 11) used mostly functional magnetic resonance imaging methods to scope brain regions related to emotion regulation and cognitive control. Three studies examined genetic or neuroendocrine markers. The evidence suggests that psychotherapy alters neural activation and connectivity of regions subserving executive control and emotion regulation. Additionally, hypoactivation in prefrontal and cingulate regions predicted treatment response. Further work in this area may inform personalised treatment approaches in clinical practice for BPD through elucidating neural mechanisms of evidence-based psychotherapy.

1. Introduction

Personality Disorders are common and debilitating mental disorders, with worldwide prevalence estimated at 6.1% (Tyrer et al., 2015). The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) proposes that the borderline subtype of personality disorder (BPD) should be made when five or more of nine diagnostic criteria are endorsed, involving primarily behavioural symptoms arising from emotion dysregulation, difficulties maintaining interpersonal relationships, impulsivity, and feelings of emptiness and identity diffusion. The clinical phenotype of BPD is heterogeneous and complex, and debate continues regarding the most appropriate way to formulate diagnosis (Grenyer, 2018; Sharp, 2016), with increasing recognition of dimensional conceptualisations (Clarkin et al., 2015; Lewis et al., 2012). BPD is associated with high suicide risk and significant functional impairment (Leichsenring et al., 2011), challenges in effective treatment provision (Grenyer et al., 2017), and extensive service utilisation with resultant high costs to society (Meuldijk et al., 2017).

A body of literature has documented neurobiological mechanisms implicated in the aetiology and maintenance of BPD, using a variety of methods including genetic, neuroendocrinology and biological, and neuroimaging (Ruocco and Carcone, 2016). Ruocco and Carcone's (2016) neurobiological model of BPD proposes the interaction of multiple systems to increase vulnerability for development of the disorder. A small number of genetics studies suggest possible associations between specific genes and BPD or BPD traits (e.g., Joyce et al., 2006; Nemoda et al., 2010; Tadić et al., 2010), while gene-environment interactions with both positive and negative environmental influences and their associated epigenetic effects create complexity in elucidating the genetic architecture of BPD (Amad et al., 2014). Recently, the first case-control genome-wide association study (GWAS) in BPD found significant genetic overlap with bipolar disorder, major depression, and schizophrenia, with implications for a potential transdiagnostic genetic factor (Witt et al., 2017). Despite these complexities, the genetic component of BPD is associated with heritability of approximately 40% and potentially over 60% (Torgersen et al., 2012), and conceivably relates to alterations in neuroendocrine and brain functioning, with the stress hormone cortisol suggested as a significant influence on observed alterations in brain structure and function (Ruocco and Carcone, 2016).

Psychotherapy is the treatment of choice for BPD and, though appropriate for the treatment of comorbid conditions, pharmacotherapy is not currently recommended as a primary therapy in published treatment guidelines (Grenyer, 2013). While a number of evidence-based psychotherapies for BPD are available and lead to symptomatic improvement (Cristea et al., 2017; Grenyer, 2013; Leichsenring et al., 2011), a central issue in the provision of effective treatment concerns

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https://doi.org/10.1016/j.neubiorev.2018.09.001
Received 16 April 2018; Received in revised form 24 August 2018; Accepted 4 September 2018
Available online 09 September 2018
0149-7634/

the approximately one-third of patients who fail to respond to treatment (McMurran et al., 2010). While there is a greater understanding of the core principles of effective treatment across different therapy approaches (Bateman et al., 2015), there is a lack of knowledge to guide the process of matching particular treatments or intervention components to particular clients to enhance treatment outcomes.

Within the medical field there is progress towards utilising neurobiological markers (biomarkers) to promote individualised care, through their status as "objective biological measures that can predict clinical outcomes" (Abi-Dargham and Horga, 2016, p. 1248). While biomarkers have the potential to refine the process of treatment selection, other benefits may also be associated with this approach. Due to the heavy reliance on behavioural symptoms to inform diagnosis and subsequent treatment selection, adopting this approach in the field of psychiatry may promote refinements in psychiatric nosology (Cuthbert and Insel, 2013). The biomarker approach also aligns with the Research Domain Criteria (RDoC) project established by the US National Institute of Mental Health (NIMH) in 2009. This initiative has progressed the identification of underlying pathophysiological processes in psychiatric disorders through the identification of neurobiological components and their manifestations and links at multiple levels of analysis across five broad domains.

Progress in the identification of biomarkers for a range of psychiatric disorders is underway (e.g., anxiety disorders: Lueken et al., 2016; posttraumatic stress disorder: Colvonen et al., 2017). The purpose of the present review is to identify and summarise all existing studies examining pretreatment biomarkers that predict psychotherapy outcomes in BPD, and also studies that document neurobiological changes associated with psychotherapy, representing the first review of this kind.

2. Methods

PRISMA guidelines informed all methods utilised in the present review. A protocol was registered on the PROSPERO international prospective register of systematic reviews and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID = CRD42017059751.

2.1. Search strategy and inclusion/exclusion criteria

Databases searched included PsycINFO, PubMed, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL), with studies published until June 30, 2018 selected. The following search terms were used: (therapy or psychotherapy or psychodynamic or schema therapy or dialectical behavior therapy or DBT or mentalisation based treatment or MBT or general psychiatric management or GPM or cognitive behavioural therapy or CBT) AND (borderline personality disorder or BPD or personality disorder) AND (biomarker or biological marker or gene or epigenetic or brain imaging or neuroimaging or hormone or neurohormonal or neurotrophin or neuroendocrine or psychophysiology or imaging or endocrine or cortisol or heart rate or heart rate variability or fMRI or MRI or PET or fNIRS or SPECT or EEG or ERP or MEG or MRS or DTI or blood flow or blood volume or skin conductance or metabolites or galvanic skin response or startle or eye blink or EMG or pupillometry or machine learning or computational psychiatry). The following inclusion criteria were applied: (a) original articles published in English following peer-review; (b) utilisation of standardised diagnostic criteria applied to an adult (18 years and over) BPD population (DSM or ICD); (c) assessment of at least one biomarker at baseline only or baseline and follow-up; (d) evidence-based psychotherapy treatment. Comorbid psychiatric diagnoses were allowed only if they were not identified as the primary diagnosis. Exclusion criteria included: (a) case studies; (b) studies that included medication augmentation.

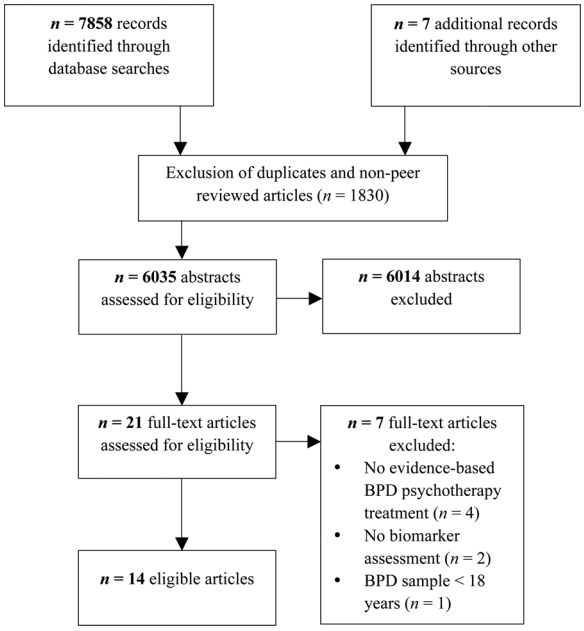

Fig. 1. Flow diagram of study selection.

2.2. Study selection

An initial search was conducted on April 13, 2017, yielding 7510 records. Duplicates, non-English records, books, theses, dissertations, and non-peer reviewed articles were removed, with 5779 records remaining and undergoing abstract review. An updated search was conducted on August 8, 2018, including records published up until June 30, 2018. This search yielded an additional 348 records, with 256 undergoing abstract review. During the abstract review, all records were independently screened by two members of the review team. When authors disagreed on study selection, a third reviewer assisted in resolution. Articles were only retained if they: (a) were original articles published in English following peer-review; (b) examined an adult BPD population; (c) investigated at least one potential biomarker assessed at baseline; (d) included evidence-based psychotherapy treatment. Following this assessment, 21 articles were retained for full-text review, which was completed by four authors. Only eligible articles as per the designated inclusion and exclusion criteria (see Section 2.1.) were retained, with 14 articles identified as appropriate (refer to Fig. 1 for a study selection flow diagram).

2.3. Data extraction

Detailed study characteristics were extracted and maintained in a table. These data included participant characteristics and diagnostic assessment methods, sample size, study design elements and methodology, biomarker category and acquisition, treatment type, follow-up timepoints, and outcomes. All findings relating to biomarker prediction of psychotherapy outcomes were included. For studies investigating biomarkers that changed after psychotherapy, baseline findings unrelated to treatment effects (e.g., neurobiological differences between groups that did not predict outcomes nor change following treatment) and longitudinal findings relating purely to non-neurobiological measures (e.g., changes on psychological self-report scales) were not considered here.

2.4. Quality assessment

The Cochrane Collaboration's Risk of Bias tool (Higgins et al., 2011) was used to assess study bias. This tool assesses bias (i.e., high, low, or

Table 1
Cochrane risk of bias assessment.

Study	Attrition Bias	Reporting Bias	Medication Reporting[a]	Inclusion/ Exclusion Criteria[b]
Driessen et al. (2009)	+	?	?	+
Goodman et al. (2014)	+	?	+	+
Knoblich et al. (2018)	+	?	+	–
Lai et al. (2007)	–	?	+	+
Mancke et al. (2017)	+	+	+	+
Niedtfeld et al. (2017)	+	+	+	+
Pérez et al. (2010)	+	?	+	+
Perez et al. (2016)	?	?	+	+
Perroud et al. (2013)	+	?	+	+
Ruocco et al. (2016)	+	?	?	+
Schmitt et al. (2016)	+	+	+	+
Schnell et al. (2007)	+	?	+	+
Viinamäki et al. (1998)	+	?	+	+
Winter et al. (2017)	+	+	+	+

Note: + = low risk of bias; – = high risk of bias; ? = unclear risk of bias, as per Cochrane criteria.
[a] Medication reporting: low risk = report no medication allowed or documentation of medication use; high risk = failure to report medication use; unclear risk = insufficient documentation of medication use to determine risk.
[b] Inclusion/exclusion criteria: low risk = inclusion and/or exclusion criteria documented; high risk = failure to report inclusion and/or exclusion criteria.

unclear) across seven domains: random sequence generation, allocation concealment, blinding of participants, incomplete outcome data, selective outcome reporting, and other biases. We only assessed bias across domains of relevance for the present review. As none of the included studies were randomised controlled trials (RCTs), and this was not considered to be critical for the purposes of this investigation, we excluded domains related to this methodology (i.e., sequence generation, allocation concealment, and blinding of participants and outcomes). The 14 included articles were assessed by two independent raters, using a third independent rater in the case of disagreements. Overall, bias was relatively low or could not be determined from the information reported in each article (see Table 1).

3. Results

3.1. Search results and characteristics of included articles

Details regarding study inclusion are provided in Fig. 1, with a total of 14 articles included in the present systematic review. These studies provided data from 467 participants diagnosed with BPD (mean sample size across studies = 33.4, range 2–115), with most studies comprising > 80% female participants. Diagnostic assessments utilised were the Structured Clinical Interview for DSM-IV (SCID-IV), Structured Interview for DSM-IV Personality Disorders (SIDP), International Personality Disorder Examination (IPDE), and Revised Diagnostic Interview for Borderlines (DIB-R). Dialectical behavior therapy (DBT) was the most common type of psychotherapy (n = 10), followed by psychodynamic psychotherapies (n = 3), while one naturalistic follow-up study included a range of treatments that varied in frequency and duration. The majority of these treatments were delivered in outpatient formats, while some studies implemented inpatient-based treatments (n = 6). Approximately one third of studies (n = 4) did not include control conditions, while other studies utilised healthy control groups (n = 6) or treatment as usual (TAU) groups (n = 1). The remaining studies including TAU in addition to healthy control groups (n = 3). The most commonly documented exclusion criteria in individual studies were history of severe psychiatric comorbidities (e.g., schizophrenia, bipolar 1 disorder), substance abuse, severe medical or neurological illness, and traumatic brain injury. Study characteristics are detailed in Table 2.

3.2. Structural neuroimaging studies

A single study by Mancke et al. (2017) used structural neuroimaging (structural magnetic resonance imaging: sMRI) to examine the effects of DBT on grey matter volume. Results indicated that the DBT vs. TAU group displayed increased grey matter volume in the rostral and dorsal right anterior cingulate cortex (ACC), inferior frontal gyrus, and superior temporal gyrus as well as altered grey matter volume in the angular and supramarginal gyrus, at follow-up. Additionally, there was an association between treatment response and increased grey matter volume in the right angular gyrus. This study provides initial evidence for the alteration of brain structure following psychotherapy for BPD. The inclusion of a TAU control condition was a strength, along with a decent sample size, albeit restricted to a single sex (female). As acknowledged by the authors, the inclusion of randomisation and an active control condition would enable further conclusions to be drawn regarding whether these findings are specifically related to DBT.

3.3. Functional neuroimaging studies

The majority of studies (n = 10) utilised functional neuroimaging methods (functional magnetic resonance imaging: fMRI: n = 7; single photon emission computed tomography: SPECT: n = 2; functional near-infrared spectroscopy: fNIRS: n = 1) during primarily affective tasks, with four studies (including the previously discussed structural neuroimaging study) linked to a shared protocol and including some participant overlap (i.e., Mancke et al., 2017; Niedtfeld et al., 2017; Schmitt et al., 2016; Winter et al., 2017). Studies are reviewed to show the development in method and approach over the past 20 years.

In the earliest study in this area, Viinamäki et al. (1998) used SPECT in a case-control design to investigate monoamine transporter density in a 1-year follow-up of a participant receiving weekly dynamic psychotherapy (vs. a participant receiving no psychotherapy during this period and with 5 healthy controls per participant). Region-of-interest (ROI) analyses investigated medial prefrontal and occipital cortices, midbrain, thalamus, and striatum, using tracers for dopamine and serotonin transporters. At baseline, the participant receiving psychotherapy displayed serotonin specific binding in medial prefrontal cortex (PFC) and midbrain areas below the control average. At follow-up, levels of both monoamines were within the average range of controls in all brain regions, indicating potential normalisation of serotonin binding. Serotonin specific binding in the medial PFC in the participant who received no psychotherapy was reported as very low at both baseline and follow-up. Dopamine specific binding of both participants was within the control average range at baseline and follow-up. Though representing a significant innovation as the first study to investigate neural correlates of psychotherapy for BPD, the constraints of this pioneering case-control study are evident. Most notably, the study is a

Table 2
Characteristics of studies ($N = 14$) investigating biomarkers in the treatment of borderline personality disorder (BPD).

Study (Country)	BPD Measure	Treatment Type (Frequency/Duration)	BPD Sample (% Female)	*N* Analysis (Control Group Type/*N*)	Biomarker	Acquisition	Timepoint Outcome Assessment	Findings
Driessen et al. (2009; Germany)	SCID-II	Index admission = inpatient DBT; baseline to FU (1 year) = 69.2% outpatient CBT or psychodynamic psychotherapy (variable frequency: range fortnightly–three sessions/week), 46% subsequent inpatient admission	$N = 13$; 100%	13 (none)	Brain activity	fMRI during recall of unresolved adverse life events (whole brain approach)	Post	- Decreased activation in right vs. left ACC and PCC, superior temporal gyrus and insula, left superior and middle frontal gyri, right medial frontal gyrus, and posterior lobe of cerebellum during recall of unresolved vs. resolved adverse life events at FU
Goodman et al. (2014; USA)	SIDP	DBT: group, individual, and additional telephone coaching (weekly/1 year)	$N = 11$; 81.8%	22 (HC: $n = 11$)	Brain activity	fMRI while viewing series of unpleasant, neutral, and pleasant pictures (ROI approach)	Post	- BPD group vs. controls displayed overall decreased amygdala activation at FU - Reduction in amygdala activity in BPD group vs. controls observed across all picture conditions, and particularly during repeated presentation of unpleasant and pleasant stimuli, and in left hemisphere - Decreased amygdala activation with repeated unpleasant stimuli associated with improved emotion regulation in BPD group
Knoblich et al. (2018; Germany)	IPDE	Inpatient DBT: (12 weeks)	$N = 44$; 84.1%	88 (HC: $n = 44$)	Methylation profile of APBA3 and MCF2	Blood samples: DNA extraction, and PCR amplification and pyrosequencing	Post	- DBT responders vs. nonresponders showed significant hypermethylation of APBA3 and MCF2 at baseline - Higher DNA methylation of MCF2 at baseline was correlated with lower global severity index scores at FU
Lai et al. (2007; Italy)	SCID-II	Psychodynamic psychotherapy: individual (weekly/16 months)	$N = 5$; 80%	7 (HC: $n = 5$)	Brain activity	SPECT: resting-state ($n = 4$ BPD group at baseline only) and psychological stress condition using psychologically violent video stimulus (whole brain approach)	Baseline ($n = 5$ BPD group; $n = 5$ HC) and post ($n = 2$ BPD group only)	- BPD group vs. controls displayed hyperperfusion of temporal, parietal, occipital, and limbic areas during baseline psychological stress condition - At FU, BPD group ($n = 2$) displayed hyperperfusion of frontal and limbic areas only
Mancke et al. (2017; Germany)	SCID-II, IPDE	Residential DBT: group, individual (12 weeks)	$N = 31$; 100%	48 (TAU: $n = 17$)	Brain structure	sMRI using voxel-based morphometry to study voxel-wise changes in grey matter volume (whole brain and ROI approaches)	Post	- DBT vs. TAU displayed increased grey matter volume in rostral and dorsal right ACC, inferior frontal gyrus, and superior temporal gyrus at FU - DBT vs. TAU displayed altered grey matter volume in the angular and supramarginal gyrus at FU (percentage change) - Treatment response (reliable change index of ZAN-BPD) was correlated with increased grey matter volume in the right angular gyrus (percentage change)
Niedtfeld et al. (2017; Germany)	SCID-II, IPDE	Inpatient DBT: group, individual (weekly/12 weeks)	$N = 28$; 100%	66 (TAU: $n = 15$ + HC: $n = 23$)	Brain activity, functional connectivity	fMRI while viewing negative or neutral picture stimuli and induced heat pain (whole brain and ROI approaches)	Post	- BPD group displayed amygdala deactivation in response to pain + negative stimuli at baseline, which was not present at FU - BPD group displayed reduced dlPFC activation in response to non-painful temperature + negative stimuli at FU - At baseline, BPD group displayed uncoupling of left amygdala and dACC in

(*continued on next page*)

Table 2 (*continued*)

Study (Country)	BPD Measure	Treatment Type (Frequency/Duration)	BPD Sample (% Female)	*N* Analysis (Control Group Type/*N*)	Biomarker	Acquisition	Timepoint Outcome Assessment	Findings
								response to pain + negative stimuli and positive connectivity in response to non-painful temperature + negative stimuli - At FU, BPD group displayed positive connectivity in response to pain + negative stimuli and negative connectivity in response to non-painful temperature + negative stimuli
Pérez et al. (2010; Spain)	SCID-II, DIB-R	DBT: group (weekly/14 weeks)	*N* = 110; 86%	110 (none)	Polymorphisms 5-HTTLPR and VNTR on SERT gene, D4.7 on DRD4 gene	Blood samples: DNA extraction	Post	- Carriers of 12-repeat allele on VNTR polymorphism of SERT displayed higher treatment adherence (i.e., lower dropout rate and longer duration of treatment) vs. non-carriers
Perez et al. (2016; USA/ Germany)	IPDE	TFP: individual (twice weekly/*M* = 12.1 months, range 10–14)	*N* = 10; 100%	10 (none)	Brain activity	fMRI during emotional-linguistic go/no-go task (ROI approach)	Post	- Increased task-related activation of right anterior dACC, dlPFC, and FPC at FU - Decreased task-related activation of vlPFC (inferior frontal gyrus: pars orbitalis and triangularis) and hippocampus at FU - Clinical improvement in constraint (MPQ) positively correlated with increased left anterior dACC activation - Clinical improvement in affective lability (ALS) positively correlated with left posterior medial OFC/ventral striatum activation, and negatively correlated with right amygdala/parahippocampal activation - Improvements in constraint predicted by baseline right dACC hypoactivation - Improvements in affective lability predicted by posterior medial OFC/ventral striatum hypoactivation
Perroud et al. (2013; Switzerland)	SCID-II	I-DBT: group, individual (daily/4 weeks)	*N* = 115; 93.9%	167 (HC: *n* = 52)	Methylation profile of BDNF CpG exons I and IV; plasma BDNF protein levels	Blood samples: DNA extraction and high-resolution melt analysis	Post	- BDNF methylation status of BPD group significantly increased at FU - DBT nonresponders accounted for the majority of the increase in methylation status, while responders showed decreased methylation status - BDNF protein levels of BPD group significantly decreased at FU
Ruocco et al. (2016; Canada/USA)	SIDP	DBT: group, individual (weekly/7 months)	*N* = 29; 90.3%	18 (none)	Brain activity	fNIRS during non-affective go/ no-go task (ROI approach)	Post	- At FU, participants overall displayed higher primarily right dlPFC activation during task vs. fixation, and also to a lesser extent in comparable region of left PFC and right medial PFC - Group with greater reductions in self-harm vs. those with least improvement displayed less right dlPFC activation at baseline, and greatest increase in activation in this region at FU (similar pattern observed in left dlPFC, but no baseline activation differences between groups)

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Table 2 (*continued*)

Study (Country)	BPD Measure	Treatment Type (Frequency/Duration)	BPD Sample (% Female)	*N* Analysis (Control Group Type/*N*)	Biomarker	Acquisition	Timepoint Outcome Assessment	Findings
								- Completers displayed less activation in left dlPFC and a smaller region in the right dlPFC at baseline vs. noncompleters during task vs. fixation - Noncompleters displayed greater activation in medial PFC/frontal pole and right inferior frontal gyrus at baseline vs. completers during task vs. fixation
Schmitt et al. (2016; Germany/ Canada)	IPDE	Inpatient DBT: group (weekly/12 weeks)	*N* = 32; 100%	56 (TAU: *n* = 16 + HC: *n* = 24)	Brain activity, functional connectivity	fMRI during reappraisal of negative and neutral pictures (whole brain and ROI approaches)	Post	- DBT group vs. controls displayed reduced anterior insula and dACC activation during reappraisal at FU - DBT group vs. controls displayed increased functional connectivity at FU during reappraisal vs. viewing of negative stimuli - DBT responders vs. nonresponders displayed diminished activity in right amygdala, ACC (subgenual, perigenual, dorsal), OFCs (medial and left), and right dlPFC during reappraisal at FU - DBT responders vs. TAU displayed reduced activation of right amygdala, right anterior insula, ACCs (subgenual, perigenual, dorsal), OFCs (medial, left inferior), and right dlPFC (middle frontal gyrus) during reappraisal at FU - DBT responders vs. non-responders and TAU displayed increased functional connectivity at FU during reappraisal vs. viewing negative stimuli
Schnell et al. (2007; Germany)	IPDE	Inpatient DBT: group (10 sessions per week/12 weeks) and individual (weekly/12 weeks)	*N* = 6; 100%	12 (HC: *n* = 6)	Brain activity	fMRI whilst viewing emotionally arousing picture stimuli (whole brain and ROI approaches)	Day 0, 7, 35, 63, 91 (DBT commenced day 8)	- BPD group vs. controls displayed more areas of increased activation at day 7, with greater activation of only posterior cingulate gyrus at day 91 FU (condition: a priori categorised high arousal stimuli) - BPD group displayed decreased activation of right ACC and left insula (over time; condition: a priori categorised high arousal negative stimuli) - BPD group displayed decreased activation of right caudal anterior and PCC, right middle temporal gyrus, and left anterior insula (over time; condition: subjectively experienced stimulus dependent arousal) - DBT responders displayed decreased activation of right inferior/medial frontal gyri, left amygdala, and bilateral hippocampus (over time; condition: subjectively experienced stimulus dependent arousal)
	SCID-II	Dynamic psychotherapy: individual (weekly/1 year)	*N* = 2; 0%	12 (HC: *n* = 10; baseline only, with	Monoamine transporter density using tracers for	SPECT: resting-state (ROI approach)	Post	- At FU, participant 1 displayed increased serotonin uptake in medial PFC and

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Table 2 (*continued*)

Study (Country)	BPD Measure	Treatment Type (Frequency/Duration)	BPD Sample (% Female)	*N* Analysis (Control Group Type/*N*)	Biomarker	Acquisition	Timepoint Outcome Assessment	Findings
Viinamäki et al. (1998; Finland)				$n = 5$ matched to each participant)	dopamine and serotonin transporters			midbrain areas compared to control average - At FU, participant 2 (who received no psychotherapy) displayed serotonin uptake in medial PFC lower than the control average
Winter et al. (2017; Germany/ Belgium)	IPDE	Residential DBT: group (weekly/12 weeks) and individual = (2 sessions/ week/12 weeks)	$N = 31$; 100%	68 (TAU: $n = 15$ + HC: $n = 22$)	Brain activity	fMRI during distraction task of negative and neutral pictures (whole brain approach)	Post	- At FU, DBT group displayed decreased right inferior parietal lobe and supramarginal gyrus activity during distraction condition, and an increase during view condition - At FU, DBT nonresponders displayed increased right ventral inferior insula activity (negative stimuli - neutral stimuli) during view condition - At FU, DBT responders displayed decreased right perigenual ACC activity in view condition vs. nonresponders - Larger decreases in BSL were associated with larger decreases in right supramarginal gyrus activity in the DBT group during distraction condition using negative stimuli - Larger decreases in ZAN-BPD were associated with larger decreases in right perigenual ACC activity in the DBT group during view condition using negative stimuli

5-HTTLPR = serotonin transporter-linked promoter region; ACC = anterior cingulate cortex; ALS = Affective Lability Scale; BDNF = brain-derived neurotrophic factor; BSL = Borderline Symptom List; D4.7 = 7-repeat allele; dACC = dorsal anterior cingulate cortex; DBT = dialectical behavior therapy; DIB-R = Revised Diagnostic Interview for Borderlines; dlPFC = dorsolateral prefrontal cortex; DRD4 = dopamine receptor D4; fMRI = functional magnetic resonance imaging; fNIRS = functional near-infrared spectroscopy; FPC = frontopolar cortex; FU = follow-up; HC = healthy controls; I-DBT = intensive dialectical behavior therapy; IPDE = International Personality Disorder Examination; MPQ = Multidimensional Personality Questionnaire; OFC = orbitofrontal cortex; PCC = posterior cingulate cortex; PCR = polymerase chain reaction; PFC = prefrontal cortex; ROI = region-of-interest; SCID-II = Structured Clinical Interview for DSM-IV Axis II Disorders; SERT = serotonin transporter; SIDP = Structured Interview for DSM-IV Personality Disorders; SPECT = single photon emission computed tomography; sMRI = structural magnetic resonance imaging; TAU = treatment as usual; TFP = transference-focused psychotherapy; vlPFC = ventrolateral prefrontal cortex; VNTR = variable number of tandem repeats; ZAN-BPD = Zanarini Rating Scale for Borderline Personality Disorder.

naturalistic follow-up of two participants, utilising a resting-state condition only.

In a similar small-scale early study, Lai et al. (2007) also used SPECT but included affective stimuli in the form of a psychologically violent video (stress condition). The treatment group ($n = 5$) received 16 months of individual psychodynamic psychotherapy vs. healthy controls ($n = 5$), who were assessed at baseline only. All but one participant in the treatment group also participated in a resting-state condition at baseline only. Of the three participants who completed treatment, two were assessed at follow-up. During the baseline psychological stress condition, the control group did not show hyper- or hypoperfused areas vs. the treatment group, who displayed hyperperfusion of temporal, parietal, occipital, and limbic areas. At follow-up, the treatment completers displayed hyperperfusion of only frontal and limbic areas during the psychological stress condition, with the authors noting that this change, as it was similar to the observed resting-state activation pattern, may suggest lower perceived psychological stress. In light of the very small sample size and the absence of control group measurement during resting-state and follow-up assessments, it is difficult to determine whether these changes are associated with psychotherapy.

Another early pilot study by Schnell and Herpertz (2007) used fMRI to investigate the effects of DBT on emotion regulation. In the condition including stimuli categorised a priori as highly arousing, the BPD group vs. controls displayed more areas of increased activation before commencing treatment, with subsequent greater activation of only posterior cingulate gyrus at day 91 vs. day 7 follow-up. When utilising highly arousing negative stimuli, the BPD group displayed decreased activation of anterior cingulate gyrus bilaterally, precentral/right middle frontal gyri, left insula, bilateral cuneus/precuneus, right posterior cingulate cortex (PCC), bilateral superior/middle temporal gyri, and right parahippocampal gyrus over time. At false discovery rate (FDR) corrected voxel level, however, only changes in right anterior cingulate gyrus and left insula regions remained. For stimuli subjectively experienced as emotionally arousing, the treatment group displayed decreased activation of caudal anterior cingulate, medial frontal/temporal gyri, PCC, right precuneus, bilateral cuneus, and left insula over time. With FDR correction, however, only changes in the right caudal anterior and PCC, right middle temporal gyrus, and left anterior insula remained. Responders displayed decreased right inferior/medial frontal gyri, left amygdala, and bilateral hippocampus activation over time in the subjectively arousing stimulus condition. The implementation of a longitudinal design including five neuroimaging timepoints and a healthy control group are strengths in this pilot study. Findings, however, must be interpreted in the context of the very small sample sizes, lack of a psychiatric control group or comparison treatment condition, and repeated measures design, which may be subject to loss of statistical power.

In a naturalistic follow-up study, Driessen et al. (2009) used fMRI during recall of unresolved adverse life events one year after recruitment during an inpatient DBT index admission. At follow-up, results indicated decreased activation in frontotemporal regions, especially the right vs. left ACC and PCC, superior temporal gyrus and insula, left superior and middle frontal gyri, right medial frontal gyrus, and posterior lobe of the cerebellum during recall of unresolved vs. resolved adverse life events. Though utilising an innovative paradigm involving personalised stimuli to evoke autobiographical memory, these findings must be interpreted in light of study limitations. These mainly concern the small sample size, lack of control group, and naturalistic follow-up, with variable types and frequency of psychotherapy occurring during the follow-up period and potentially influencing results.

Goodman et al. (2014) used fMRI to investigate the effects of DBT on processing of affective stimuli, with the amygdala identified as the ROI. Decreased amygdala activation was observed at follow-up, evident across all picture conditions, and was associated with improved self-reported emotion regulation. However, this study is also subject to limitations regarding small sample sizes and the inclusion of healthy control comparison only. Furthermore the inclusion of a "passive" emotion regulation task, as acknowledged by the authors, may not necessarily most accurately capture the neural correlates of DBT, in that it significantly focuses on imparting "active" emotion regulation skills. In contrast, Schmitt et al. (2016) used fMRI to investigate neuroimaging correlates of an explicit emotion regulation strategy following DBT, using an "active" reappraisal task. At follow-up, the DBT group vs. controls displayed reduced anterior insula and dorsal ACC (dACC) activation during reappraisal (ROI analyses) and increased functional connectivity during reappraisal vs. viewing negative stimuli. DBT responders vs. nonresponders displayed reduced right amygdala, ACC (subgenual, perigenual, dorsal), medial and left orbitofrontal cortex (OFC), and right dorsolateral PFC (dlPFC) activation during reappraisal at follow-up (ROI analyses), while at the whole-brain level DBT responders displayed decreased subgenual ACC activation. DBT responders vs. TAU displayed reduced activation of the right amygdala, right anterior insula, ACC (subgenual, perigenual, dorsal), medial and left inferior OFC, and right dlPFC (middle frontal gyrus) during reappraisal at follow-up (ROI analyses), while at the whole-brain level DBT responders displayed reduced activation of subgenual ACC and superior frontal gyrus. Additionally, at follow-up DBT responders vs. nonresponders, as well as TAU, displayed increased functional activity during reappraisal vs. viewing negative stimuli.

While most of the included studies utilised affective stimuli, Ruocco et al. (2016) used fNIRS to investigate prediction of psychotherapy outcomes through PFC activation during a cognitive inhibition task in patients who were actively self-harming. Following DBT, treatment completers displayed less bilateral dlPFC activation at baseline during task condition compared to cross-hair fixation. At follow-up, all participants displayed higher primarily right dlPFC activation during the inhibition task, also evident to a lesser extent in a comparable region of the left PFC and right medial PFC. Participants with greater reductions in self-harm vs. those with least improvement displayed less right dlPFC activation at baseline, and also the greatest increase in activation in this region at follow-up. A similar pattern was observed in the left dlPFC, however there were no baseline activation differences between those with greater or lesser reductions in self-harm. Treatment completers vs. noncompleters displayed less activation in the left dlPFC, and also in a smaller region in the right dlPFC, at baseline during the inhibition task. Compared to those who completed treatment, noncompleters displayed greater baseline activation in the medial PFC/frontal pole and right inferior frontal gyrus during the inhibition task. It is important to consider these findings in light of the absence of control conditions and recruitment of a BPD sample accessing regular clinical services with high levels of psychiatric comorbidities. Of note, this was the only included study to utilise fNIRS, a method with potential for clinical translation, as highlighted by the authors.

A more recent small-scale study specifically investigating transference-focused psychotherapy was conducted by Perez et al. (2016), who used fMRI during a cognitive-affective inhibition task. After treatment, increased task-related activation of the dACC, dlPFC, and frontopolar cortex was observed relative to baseline. Conversely, there was decreased activation of the ventrolateral PFC (vlPFC; inferior frontal gyrus: pars orbitalis and triangularis) and hippocampus at follow-up. Clinical improvement in constraint, measured by the Multidimensional Personality Questionnaire, was positively correlated with increased left dACC activation and predicted by baseline right dACC hypoactivation. Clinical improvement in affective lability, measured by the Affective Lability Scale, was positively correlated with left posterior medial OFC and ventral striatum activation, and negatively correlated with right amygdala/parahippocampal cortex activation. Baseline right dACC hypoactivation predicted improvement in affective lability. Though an important contribution to the initial literature on neural correlates of psychodynamic psychotherapy for BPD, the small sample size and absence of a control group render these findings as preliminary.

Niedtfeld et al. (2017) investigated the effects of DBT with a focus on the role of pain in emotion regulation. Significantly, this study overcame some limitations of previous studies through inclusion of healthy controls as well as a BPD group receiving TAU. The DBT group displayed amygdala deactivation in response to negative stimuli paired with pain at baseline, and this effect was not present after treatment. At follow-up, the DBT group displayed reduced dlPFC activation in response to non-painful temperature paired with negative stimuli. With regards to functional connectivity, at baseline the DBT group displayed uncoupling of left amygdala and dACC in response to pain paired with negative stimuli and positive connectivity in response to baseline temperature paired with negative stimuli. Following treatment, the DBT group displayed positive connectivity in response to pain paired with negative stimuli and negative connectivity in response to baseline temperature paired with negative stimuli, indicating a reversal of connectivity patterns at follow-up relative to baseline. Notably, this study is the first to investigate the effects of psychotherapy on the neural correlates of pain perception in BPD.

Building on the work of Schmitt et al. (2016); Winter et al. (2017) used fMRI to examine the neural correlates of another explicit emotion regulation strategy in the context of DBT: distraction. At follow-up, the DBT group displayed decreased right inferior parietal lobe and supramarginal gyri activity during the distraction condition and, conversely, an increase in activation of these areas in the view condition. DBT nonresponders vs. responders displayed increased right ventral inferior insula activity during the view condition (negative stimuli - neutral stimuli). DBT responders vs. nonresponders displayed decreased right perigenual ACC activation during the view condition. Larger decreases in the Borderline Symptom List were associated with larger decreases in right supramarginal gyrus activity in the DBT group during the distraction condition (negative stimuli). Larger decreases in the ZAN-BPD were associated with larger decreases in right perigenual ACC activity in the DBT group during the view condition (negative stimuli). In interpreting the findings of Schmitt et al. (2016) and Winter et al. (2017), it is important to consider that participants in the BPD TAU groups received a range of treatments that were not necessarily matched to the DBT treatments investigated and, as acknowledged, may better control for time rather than general psychotherapy effects. Despite this, the strengths of these studies include decent sample sizes, though restricted to the female sex, and inclusion of treatment as usual and healthy control comparison groups.

3.4. Genetics and neuroendocrine studies

Three studies investigating the relationship between genetic factors and psychotherapy for BPD (i.e., DBT) were identified. One investigated specific genetic polymorphisms, while the other two examined methylation profiles.

Pérez et al. (2010) investigated the role of SERT and DRD4 genes on DBT psychotherapy adherence, with a specific focus on polymorphisms 5-HTTLPR, VNTR, and D4.7. Carriers of the 12-repeat allele on the VNTR polymorphism of SERT displayed greater adherence to treatment vs. non-carriers (i.e., lower rate of dropout and longer duration of treatment). No associations between psychotherapy adherence and other polymorphisms were found.

In the first study of methylation profiles in the context of psychotherapy for BPD, Perroud et al. (2013) examined methylation profiles of brain-derived neurotrophic factor (BDNF) CpG exons I and IV, and plasma BDNF protein levels, also in the context of DBT treatment. BDNF methylation status of the treatment group significantly increased at follow-up, while BDNF protein levels decreased. Nonresponders predominantly accounted for this increase in methylation status, while responders displayed a decrease. Methylation status changes were also associated with self-reported changes in depression, hopelessness, and impulsivity. Following on from this study, Knoblich et al. (2018) investigated the methylation profiles of APBA3 and MCF2. DBT responders vs. nonresponders showed significant hypermethylation of APBA3 and MCF2 at baseline, suggesting their potential as epigenetic biomarkers to assist in predicting response to treatment. Higher methylation of MCF2 at baseline was also correlated with lower global severity index scores at follow-up.

4. Discussion

The current review aimed to provide a systematic overview and synthesis of the research investigating biomarkers that predict evidence-based psychotherapy outcomes for BPD and neurobiological characteristics that are altered by psychotherapy. In line with the PRISMA guidelines, our search strategy identified 14 articles ($n = 11$: neuroimaging; $n = 3$: genetics), reflecting the early developmental stage of the field. Several factors complicate the process of synthesising findings to arrive at broad conclusions; most notably, the very small number of studies in the field at this point in time, lack of RCTs, lack of control or comparison groups in some studies, variety of neuroimaging tasks and paradigms, and differences in modality, frequency, and duration of psychotherapy. Broadly speaking, however, a number of brain regions were consistently implicated across studies. Most notably, decreased activity of the anterior cingulate, amygdala, insula, and PFC, especially in ventrolateral and right hemisphere regions, was observed following psychotherapy treatment. Increases in PFC, particularly dlPFC, and dACC activation were also observed following psychotherapy. Hypoactivation of prefrontal, especially dlPFC and cingulate areas tended to predict response to psychotherapy, with greater increases in dlPFC activity, greater functional connectivity, and reduced activation of limbic areas at follow-up generally associated with better treatment outcomes. The single structural neuroimaging study identified in the current review is in accordance with these functional findings. Most notably, increased grey matter volume in the right ACC, inferior frontal gyrus, and superior temporal gyrus, as well as altered grey matter volume in the supramarginal gyrus. As only three genetics studies were identified in the current review, the role of genetic factors in the treatment of BPD requires further large-scale studies to expand the state of knowledge regarding genetic influences on psychotherapy outcomes. At best, the biomarker correlates identified in the current review provide initial evidence for changes in patterns of brain activity and the first documentation of structural brain changes in areas associated with regulation of emotion and executive control following psychotherapy. There is some indication that psychotherapy treatment response may be predicted through patterns of neural activation in these regions at baseline and initial evidence for epigenetic biomarkers of psychotherapy treatment response. The following discussion will provide more detailed interpretation of why these brain regions may be implicated, in light of existing neurobiological research regarding aetiology and symptomatology of BPD. Given that neuroimaging studies were predominantly identified in the present review, greater emphasis on these findings is warranted.

4.1. Neuroimaging findings and a neurobiological model of BPD

The neuroimaging findings in the current review concerned both neurobiological changes as a result of psychotherapy treatment, and biomarkers that predict treatment response. The very small number of studies in this area creates difficulties in synthesising a coherent picture of implicated brain regions, which will hopefully be clarified with further progress in the field. Early studies utilised case-control designs and very small sample sizes, which also limits the generalisability of findings. A related issue concerns the evolution of neuroimaging methods, and technical differences in earlier studies relative to more recent ones that may impact findings. With this in mind, the focus here will be on interpreting findings that consistently emerged across studies, through contrast with a recent model of the neurobiology of BPD (Ruocco and Carcone, 2016).

Five primary domains of fMRI research in the neurobiology of BPD have been identified: emotion perception, emotion regulation, emotion-cognition interactions, resting-state, and pain sensation (Ruocco and Carcone, 2016). In the present review, the majority of identified neuroimaging studies utilised paradigms linked to the perception and regulation of emotions (with a lesser focus on emotion-cognition interactions, cognition alone, and resting-state paradigms). The focus of studies included in the present review can be understood in regard to broad treatment targets of psychotherapy for BPD – typically addressing symptoms related to emotion dysregulation and impulsivity.

Consistent with the aim of psychotherapy to increase emotion regulation capacity in BPD, the current review identified decreased brain activation following psychotherapy in anterior cingulate and prefrontal, particularly right hemisphere, regions. These changes may reflect increased emotion regulation capacity in light of the role of the ACC in regulation of both cognitive and affective processing of stimuli (Bush et al., 2000). It is proposed that dorsal-caudal and ventral-rostral subregions form distinct but interrelated networks with the medial PFC and play a key role in emotion regulation (Etkin et al., 2015, 2016; Etkin et al., 2011). Strategies that promote the down- and up-regulation of emotion consistently recruit the vlPFC and PCC, with down-regulation more strongly associated with right-lateralised activity (Morawetz et al., 2017). Additionally, the dACC may be specifically implicated in evaluation of the perceived benefits of exerting cognitive control and determining the magnitude of effort to be allocated (Shenhav et al., 2013). This may reflect a potential neural mechanism of a common goal of psychotherapy for BPD patients: fostering greater capacity to exert control over habitual and impulsive responses often related to emotion dysregulation. The current review identified studies that found both increased (e.g., Perez et al., 2016) and decreased (e.g., Schmitt et al., 2016) activity of the dACC following psychotherapy, as well as increased functional connectivity of networks including this region (e.g., Niedtfeld et al., 2017; Schmitt et al., 2016), with hypoactivation in this area predicting response to psychotherapy (Perez et al., 2016). These preliminary findings suggest a broad role of this region as a target of psychotherapy, and also the potential that individual differences in pre-treatment activation levels may influence psychotherapy response, with greater functional connectivity conceivably a neural marker of effective psychotherapy outcomes.

Reduced activation of the amygdala, but also certain prefrontal and parietal areas following psychotherapy was identified in the present review. These findings are consistent with prior BPD research suggesting greater activity in limbic and frontotemporal regions in response to emotional stimuli (Beblo et al., 2006; Guitart-Masip et al., 2009; Minzenberg et al., 2007; Schnell et al., 2007), and point toward the role of psychotherapy in normalising hyperactivation in these regions. With regard to amygdala activation in BPD there are discrepancies in the field, with conflicting findings of two recent meta-analyses. The first reported that processing of negative emotions elicits greater insula and PCC activation, but reduced amygdala activation (Ruocco et al., 2013), while the following review found evidence for hyperactivity of amygdala response (Schulze et al., 2016). These discrepancies may be related to differences in methodological characteristics of included studies and meta-analytic strategy, however Ruocco and Carcone (2016) propose that they may be related to the amygdala's role in evaluating relevance of stimuli in the context of an individual's motivation and goals, particularly in ambiguous contexts that may be associated with potential threat (Cunningham and Brosch, 2012). In addition to this, studies of functional connectivity in BPD show greater interconnection between amygdala and ACC during processing of negative emotion (Cullen et al., 2011) and reduced functional connectivity at resting-state between amygdala and regions essential for effective emotion regulation (Baczkowski et al., 2017).

To better understand these complex preliminary findings, future studies may benefit from the inclusion of designs that focus on connectivity between several brain regions and also multimodal assessment to scope the interactive role of other neurobiological systems in treatment response more broadly.

4.2. The role of genetics in the neurobiology of BPD and treatment response

Genetic components in the pathogenesis of BPD account for an estimated heritability of 40%, yet findings are sparse at this point in time and a complex picture is emerging, with a recent model proposing that the balance of environmental support/enrichment factors and risk factors influence plasticity genes, rather than specific vulnerability genes alone (Amad et al., 2014).

With only three studies identified that investigate the role of genetics in BPD psychotherapy response, much work in the field remains. In saying this, the role of epigenetic modifications in the pathophysiology of BPD, particularly those related to childhood trauma, point toward a promising opportunity for further investigation of methylation status of multiple genes in BPD (Bassir Nia et al., 2018; Dammann et al., 2011; Teschler et al., 2016). Preliminary findings in the present review suggest that methylation status of the BDNF gene may be altered through psychotherapy, crucially influencing dynamic fluctuations in cognition (Perroud et al., 2013). Furthermore, findings identify methylation profiles of APBA3 and MCF2 as the first example of potential epigenetic biomarkers to predict psychotherapy treatment response. Further research will clarify how epigenetic biomarkers may predict psychotherapy response and can be targeted through psychotherapy to influence cognition, relating to the possibility of cognitive markers as endophenotypes (Koudys et al., 2018). A recent review by Jiménez et al. (2018) presents evidence for the relationship between psychotherapy and epigenetic changes, highlighting the complexities of the mind-brain connection and advocating an "integrative multilevel approach including a focus on gene-environment interaction, epigenetic regulation, and subjective experience" (p. 2) in order to gain a sophisticated understanding of psychotherapy mechanisms of change.

4.3. Limitations and future directions

Certain limitations, not only with regard to the scope of the current review, but also in terms of complexities within the field, must be considered. As already mentioned, the number of studies identified in the present review was very small, with the first psychotherapy biomarker study in BPD conducted in 1998. Since this time, the field has shown an exponential increase in growth, with half of identified studies published in roughly the past two years alone. The findings in the current review must be regarded as preliminary in terms of any consistent patterns of neurobiological changes and specific biomarkers that predict psychotherapy outcome. An overarching complexity within BPD research more broadly concerns the high levels of diagnostic heterogeneity and overlapping psychiatric comorbidities encountered. This was certainly evident in the present review, with high levels of psychiatric comorbidities documented. Some studies suggest that inclusion of BPD samples accessing regular clinical services and high in comorbidities is a limitation, but others argue this more accurately captures the reality of complexity encountered in clinical practice. We recommend that future psychotherapy research investigating biomarker correlates, continue to include thorough diagnostic assessment in order to further explore the multifarious nature of BPD. In addition, utilising clinical assessments based on new methods that capture trait dimensions of personality disorder in addition to traditional diagnostic criteria may provide fresh insights into the nature of the disorder and arising diagnostic considerations.

With regard to study methodology, while the included studies were generally rated as low risk in terms of bias and study quality, no RCT studies were identified. While this may be related to complexities within the field of clinical BPD research, larger RCT studies may help to strengthen biomarker findings and ascertain possible intervention-specific effects. It remains a question of future biomarker research to

uncover whether neural correlates may differ as a function of intervention type (e.g., DBT vs. psychodynamic approaches), or whether these findings generalise across different types of psychotherapy. The included studies also differed considerably in terms of other methodological aspects; for example, treatment frequency and duration and definitions of treatment response.

On a related note, as biomarker findings accumulate across diagnostic groups in the literature more broadly, the question arises as to whether a potential transdiagnostic component may exist (e.g., Pinto et al., 2017), reflecting overlapping neurobiological factors related to the pathophysiology of psychiatric disorders. Further discoveries in this area may benefit psychiatric nosology in general but may hold particular relevance for the personality disorder field. This is in the context of the high incidence of comorbid personality disorder diagnoses, and the ongoing debate regarding categorical vs. dimensional conceptualisations. A general factor ('g') of personality pathology has been identified at the phenomenological level of diagnostic criteria (Sharp et al., 2015), and this may be connected to core neurobiological factors that are common across personality disorder diagnoses and associated with pathogenesis of the disorder.

Greater clarity in the conceptualisation of personality disorder diagnosis, and the development of a nosological system based on underlying neurobiological factors rather than presenting symptoms only, can be guided by the accumulating knowledge in the field of biomarker and neurobiological mechanism research (see Winsper, 2018 for a recent review on the aetiology of BPD). Further research in this area has the potential to shed light not only on core neurobiological vulnerabilities related to the pathogenesis and maintenance of BPD, but also on the mechanisms of action through which psychotherapies exert beneficial outcomes. For example, Herpertz et al. (2018b) recently proposed that the neurobiological mechanisms of emotion dysregulation may serve as a treatment target through which psychotherapy, the neuropeptide oxytocin (e.g., Bertsch et al., 2013; Lischke et al., 2017), and other novel interventions such as neurofeedback (e.g., Paret et al., 2016) and cognitive training may be used to enhance emotion regulation. Neurobiological and behavioural correlates of emotion dysregulation in BPD have been documented (Bertsch et al., 2018) and further investigation of the links between these domains, and mechanisms of psychotherapy in enhancing emotion regulation may be a fruitful area of future research. There are multiple evidence-based psychotherapy models for the treatment of BPD and it may be informative to ascertain whether different theoretical approaches possess common or distinct pathways through which they produce beneficial effects (for a review of the effects of psychotherapy on brain function more broadly: Barsaglini et al., 2014; Fournier and Price, 2014). Another related question concerns whether psychotherapy is "more than the sum of its parts" and the potential role for common neurobiological mechanisms, in parallel with the argument for common effective factors across psychotherapy modalities (Wampold, 2015). This is particularly relevant in regard to the literature that has investigated neurobiological correlates of specific strategy training in BPD (e.g., Dixon-Gordon et al., 2017; Koenigsberg et al., 2009; Metcalfe et al., 2017; Schulze et al., 2011; Silvers et al., 2016) and further research that may inform the design of individualised modular approaches for the treatment of BPD.

While the accumulation and clinical translation of studies investigating biomarker correlates of psychotherapy will take significant time to advance, the ideal is the development of greater precision in diagnosis and treatment selection. A significant benefit of research efforts that pursue this aim is potential for the discovery of predictive biomarkers that are relevant for the *individual* patient and can enhance the process of clinical decision-making. Fostering the development of such a "personalised medicine" approach to psychotherapy treatment for BPD is particularly important in light of the severity of the condition and rates of nonresponse to treatment.

A further area of future research relates to the increased awareness of emerging personality disorder symptoms and efforts towards prevention and early intervention in adolescence (Chanen et al., 2017; Sharp and Fonagy, 2015). While there is some research into neurobiological bases underlying early manifestations of BPD symptoms (Ensink et al., 2015; Goodman et al., 2013), relatively less is known in contrast to the adult literature. One study, however, provides initial evidence for the use of biomarkers in adolescent BPD through investigating longitudinal changes in resting cardiac function in adolescent non-suicidal self-injury (Koenig et al., 2018). Further work examining potential biomarkers and neural correlates of psychotherapy in this population could contribute to the development of effective forms of early intervention and also the detection of vulnerability factors and efforts aimed at prevention. To this end, there may be a particularly beneficial role for psychotherapy during developmentally sensitive periods (Jiménez et al., 2018).

The value of integrative neurobiological research into BPD that cuts across and elucidates causal links between multiple domains has been emphasised (Carcone and Ruocco, 2017; Etkin, 2018; Meyer-Lindenberg, 2012; Ruocco and Carcone, 2016) and represents a promising avenue for future investigation. There is some initial work in this area; for example, an imaging-genetics study found a significant association between the BDNF 66Met allele and deficits in amygdala habituation (Perez-Rodriguez et al., 2017). In addition to exploring the links between multiple systems, another promising direction of future research concerns neurobiological substrates of the social-cognitive deficits linked to relational interaction in BPD (Bourke and Grenyer, 2017; Lazarus et al., 2014; Minzenberg, 2017). For example, using an innovative 2-person neuroimaging paradigm to investigate cross-brain information flow between dyads in real-time, Bilek et al. (2017) found reduced neural coupling in BPD and healthy control dyads, but also the reversal of these deficits for patients in remission. These findings underscore the importance of novel methodological approaches, such as imaging real-time interactions between patients and others, to discover biomarkers for BPD that may not otherwise be detected through more traditional neuroimaging paradigms. BPD can be understood as involving core relational difficulties, both intrapersonally and interpersonally (Grenyer, 2014), with associated neural correlates (Herpertz et al., 2018a, 2014). It is noteworthy to consider the lack of neuroimaging paradigms in the present review that scope these dynamic social-affective processes. Social interaction has recently been proposed as a central – and possibly even principal – mode of the human brain, warranting an explicit focus on interactive relational paradigms in neuroscience (Hari et al., 2015). Not all laboratories have access to hyperscanning methodologies (see Astolfi and Babiloni, 2014 for a review) and the technology and accessibility of these methods will continue to develop. There are, however, elegant and innovative paradigms to scope social processes developed for single-scanner contexts (e.g., van Schie et al., 2018). As the complexity and volume of data expands, the use of computational psychiatry methods may benefit future BPD research examining the complex links between neurobiological systems, levels of analysis, and neural correlates of interpersonal interactions (Fineberg et al., 2017; Huys et al., 2016). As an example, one potential avenue for integrative clinical social neuroscience research could investigate the neural correlates of expressive language disturbance in BPD (Carter and Grenyer, 2012a, b).

5. Conclusion

At present, psychotherapy represents the most effective, evidence-based treatment for BPD. Though we have a greater understanding of the common effective elements of clinical practice across treatment modalities (Bateman et al., 2015), we understand very little about the underlying neurobiological mechanisms of psychotherapy. Knowledge of neurobiological factors underlying BPD is advancing and, in combination with the increase in studies examining neural correlates of psychotherapy for BPD, the field may gradually move toward greater precision in diagnosis, clarifying the neural mechanisms of

psychotherapy, and improved outcomes through personalised treatment.

Conflicts of interest

None.

Funding

None.

Acknowledgements

The authors wish to acknowledge the Project Air Strategy for Personality Disorders supported by the NSW Ministry of Health.

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