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Protocol article: Developing and validation of an emotional picture set of self-injury (EPSI) for Borderline personality disorder

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Abstract

Introduction: Borderline personality disorder (BPD) is a severe psychiatric disorder that is characterized by major problems in emotion regulation. Affected persons frequently engage in non-suicidal self-injury (NSSI) to regulate emotions. NSSI is associated with high emotionality in BPD patients and it can be expected that stimuli depicting scenes of NSSI elicit an emotional response distinctive for BPD. The current study protocol describes the development and validation of an emotional picture set of self-injury (EPSI) to advance future research on emotion regulation in BPD.

Methods and analysis: The current case-controlled experiment aims to develop and validate an emotional picture set relevant for BPD. Emotional response to EPSI as well as to a neutral picture set will be investigated in a sample of 30 BPD patients compared to 30 matched, healthy controls and to 30 matched depressive controls. Emotional response will be assessed by heart rate variability (HRV), facial expression and self-assessment manikin (SAM).

Ethics and dissemination: Ethics approval was obtained by the medical ethics committee of the Carl-von-Ossietzky University of Oldenburg, Germany (registration: 2017-044). Results of the main trial and each of the secondary endpoints will be submitted for publication in a peer-reviewed journal.

Trial registration number: clinicaltrials.gov: NCT03149926

Keywords: Borderline, Emotion regulation, Emotional stimuli, NSSI

Article Summary

This study aims to develop and validate an emotional picture set for BPD. Previous research suggests that to reliably elicit an emotional response emotional stimuli material has to tap into disorder-relevant emotional themes. NSSI has been strongly connected to BPD symptomatology and can be expected to elicit a distinct emotional response in persons with BPD. The purpose of the current study is to create the first standardized image database depicting scenes of NSSI (EPSI) and in a second step to validate the database in a sample of persons with BPD, a depressive control group, and a healthy control group. The availability of a standardized and BPD relevant emotional picture set is a valuable tool to advance clinical as well as neuroimaging research on emotion regulation in BPD.

Strength and limitations of this study

- Controlled study design to develop emotional stimuli relevant for BPD
- Emotional reaction is assessed by subjective as well as objective measurements
- Emotion evocation is limited to NSSI however other emotional trigger (e.g. social interaction) are not investigated
- Limited to BPD patients that actually engage in NSSI

Introduction

Borderline personality disorder (BPD) is a severe psychiatric disorder that is characterized by impairments in interpersonal, cognitive, and emotional functioning (APA, 2013; Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004). Pervasive problems in affect regulation have been identified as the central area of dysfunction in BPD. BPD even has been conceptualized as a disorder of the emotion regulation system (Linehan, 1993). Emotion dysregulation comprises high emotional vulnerability in conjunction with an inability to regulate emotions. Emotional vulnerability in individuals with BPD is characterized by high sensitivity to emotional stimuli, unusual emotional intensity and a slow return to emotional baseline (emotions are long lasting). In addition, the identification, expression, and inhibition of emotions are impaired (Linehan, 1993; J. Svaldi, C. Dorn, S. Matthies, & A. Philipsen, 2012).

Not surprisingly, emotional evocative material is commonly used to investigate BPD pathology. Previous studies have employed various emotional stimuli such as emotional facial expression (Baskin-Sommers et al., 2015; Cullen et al., 2016), pleasant or unpleasant pictures (Hazlett et al., 2012; Suvak et al., 2012), pictures and video clips depicting social interactions (Koenigsberg et al., 2009; Lobbestael & Arntz, 2015) or script driven imagery of an act of self-injury (Kraus et al., 2010). However, research findings on emotion regulation in BPD to date are inconsistent in terms of evoking emotional responses in BPD patients (Sloan et al., 2010; van Zutphen, Siep, Jacob, Goebel, & Arntz, 2015). While some studies did not find evidence for abnormal emotional responsiveness in BPD (Feliu-Soler et al., 2013; Kuo & Linehan, 2009; Suvak et al., 2012) others did (D. Eddie & M. E. Bates, 2017; Kraus et al., 2010; C. Sauer, E. A. Arens, M. Stopsack, C. Spitzer, & S. Barnow, 2014). One possible explanation for these contradictionary results might be that the stimulus material was not specific enough to elicit an emotional response in persons with BPD. For example, in a recent study that addressed the potential difference in emotional response depending on the specificity of the presented stimuli baseline emotional intensity and emotional reactivity in BPD patients were compared to healthy controls. Emotional response to six discrete emotion-eliciting film clips was evaluated by means of physiological and subjective reactions. Furthermore, the two groups were compared regarding their emotional reaction to films containing content associated with BPD (e.g. sexual abuse, emotional dependence, and abandonment/separation). Compared to healthy controls, persons with BPD did not show subjectively heightened reactivity to most of the discrete emotion-eliciting films but a significant stronger emotional response on "BPD-specific content" films (C. Sauer et al., 2014). Those findings suggest that measuring emotion dysregulation in BPD might only arise in contexts that are psychologically challenging (Sloan et al., 2010; Suvak et al., 2012). The

actual emergence and intensity of emotions depend on an array of psychological characteristics of the person such as personality, learning experiences and cognition, the situational context but also on the type and intensity of the perceived stimulus (Kučera & Haviger, 2012). Emotional stimuli that activate specific, self-relevant information seem to arouse a more intense emotional reaction than more general emotional stimuli (Philippot, Schaefer, & Herbette, 2003). Therefore, to elicit a distinctive and BPD specific emotional response the stimulus material has to have a high relevance for persons with BPD and has to trigger sensitivities distinct for BPD (Suvak et al., 2012). Such a triggering event could be the presentation of material used for non-suicidal self-injury (NSSI).

NSSI is associated with clinical and functional impairments and occurs in a variety of psychiatric disorders (Zetterqvist, 2015). There is an ongoing scientific debate regarding the conceptualization and diagnostic organization of NSSI. The fifth version of the Statistical and Diagnostic Manual of Mental Disorders (DSM-5) presents Non-Suicidal Self-Injury Disorder (NSSID) as a separate nosological entity however as a condition that requires further investigation (Association, 2013; Zetterqvist, 2015). This shows that NSSI is not unique to BPD. However, there is a general consensus that NSSI is related to BPD and can be considered as a core symptom of the disorder (APA, 2013; Zetterqvist, 2015). NSSI is defined as the deliberate destruction of healthy body tissue that is not suicidal in nature. About 90% of patients with BPD do engage in NSSI (Zanarini et al., 2008). NSSI typically includes repeated behaviors, such as skin cutting, banging or hitting, burning, scratching, and interfering with wound healing (Favazza, 1998). Emotion dysregulation is closely linked to NSSI in persons with BPD. According to the experiential avoidance model, NSSI is applied to reduce or remove aversive emotional experiences and might be maintained by negative reinforcement (Chapman, Gratz, & Brown, 2006; Nock & Prinstein, 2004; Reitz et al., 2015).

Empirical evidence suggests that NSSI is commonly performed as emotion regulation strategy. Self-injurers use NSSI to reduce unpleasant feelings, overcome dissociation, for self-punishment or for the reduction of aversive inner tension (Andover & Morris, 2014; E. D. Klonsky, 2007). Typically, NSSI is preceded by high arousal of negative emotions whereas NSSI behavior is associated with a decrease in these emotions (E. D. Klonsky, 2007; Victor & Klonsky, 2014). For example, a decrease in negative affect and arousal was observed in self-injurers that were asked to visualize cutting or to engage in another painful behavior whereas the performance of a non NSSI-related task did not lead to a decrease (E. D. Klonsky, 2007). In addition, seeing blood during NSSI seems to be an important aspect for many self-injurers. Glenn and Klonsky (2010) investigated the role of seeing blood during NSSI in persons with a history of NSSI. Most participants (51.6%) reported seeing blood during NSSI was important. Furthermore, participants reported that seeing blood fulfilled multiple functions

such as, to relieve tension (84.8%), to calm down (72.7%), to feel real (51.5%), to show the realness of NSSI (42.4%), to help focus (33.3%) and to show that NSSI has been performed correctly/deep enough (15.2%). A pilot study by Naoum et al. (2016) compared 20 female BPD patients and 20 healthy controls (HC) to investigate the effect of seeing blood during NSSI following stress and pain induction. The BPD patients showed a significantly stronger decrease in arousal than the HC group, however with no significant effects between blood and non-blood conditions. In addition, the urge for NSSI, significantly greater decreased in the blood condition in BPD patients. While, seeing blood did not bring greater tension relief.

Despite the connection of deficient emotion regulation and NSSI in BPD, yet no study is available that uses stimuli depicting different stages of NSSI to investigate whether the emotional reaction of BPD patients is gradually dependent on the stage of NSSI shown by the stimuli. A specified stimuli-database, validated in a BPD population for evoking emotional responses in BPD is however lacking.

This Study

Although emotion dysregulation is recognized as a core symptom of BPD, current evidence is inconsistent and contradictionary. This could be, at least partially, explained by the use of unsuitable and unspecific emotional stimulus material that does not tap into BPD-relevant themes. However, to improve and extend research on emotion regulation in BPD the availability of validated emotional stimuli that reliably elicit emotional reactions distinct for BPD is a necessary prerequisite.

This study aims to develop and validate an emotional picture set, EPSI (emotional picture set with scenes of self-injury), relevant for BPD. In a second step, the emotional reaction will be assessed by means of a self-report measurement as well as by a psychophysiological assessment of the emotional reaction in a sample of persons with BPD who engage in NSSI, in a depressive control group and in a sample of matched healthy controls. Furthermore, participants are asked to indicate how strong the pictures relate to their person or biography. EPSI depicts objects frequently used for NSSI and show the application of those objects at different stages of NSSI (pre-NSSI, NSSI, post-NSSI). As NSSI can be associated with different emotional reactions depending on the stage of NSSI, differences in the emotional reaction are expected for persons with BPD for the specific NSSI categories. In a pre-NSSI stage (preparing for NSSI), negative affect, arousal and tension are expected to be strongest. When starting NSSI, negative affect, arousal and tension might start to decrease. On a post-NSSI stage (successfully performed NSSI, seeing blood), an even stronger decrease of emotions and a sense of relief and relaxation is expected. It is hypothesized that the control groups show the opposite emotional reaction with lowest emotional response when seeing

pictures of a pre-NSSI stage and strongest emotional response when watching post-NSSI pictures. Furthermore, BPD participants are expected to report higher self-reference regarding the pictures in comparison to the healthy controls.

To investigate if our database is BPD relevant, the evaluations of the NSSI images will be compared to neutral images and also to two different control groups. This study allows for investigating to what extent EPSI can elicit an emotional response distinctive for persons with BPD and if the emotional response differs with regard to the stage of NSSI.

Objectives

Primary outcome variables are self-rated emotional reaction measured with the Self-Assessment-Manikin (SAM, (M. M. Bradley & P. J. Lang, 1994)); psychophysiological measurements of emotion will be assessed by heart rate variability (HRV) as indicator of Autonomic Nervous System (ANS) activity and the analyses of facial expression as measured with Noldus FaceReader software (Noldus Information Technology, www.noldus.com). As a secondary outcome variable, Self-reference of EPSI will be measured on a 5-point Likert-scale with the item 'How much do you see a relation to your own person/ to your biography?' from 1 (not at all) to 5 (very much) (C. Sauer et al., 2014).

Primary objectives:

1. To determine a BPD symptomatic-relevant stimuli-set, an image database of NSSI will be created and validated (EPSI).
2. To identify whether EPSI elicit a stronger emotional reaction in individuals with BPD having a history of NSSI, the emotional reaction to EPSI will be compared within group-wise to the emotional reaction to neutral stimuli and between group-wise to healthy controls and to depressed patients .

Secondary objectives:

1. To assess the extend, to which the emotional reaction on EPSI in persons with BPD that engage in NSSI is gradually dependent when seeing pre-NSSI, NSSI, and post NSSI pictures.
2. To investigate if persons with BPD that engage in NSSI rate EPSI as more self-referential than matched healthy controls and depressive controls do.
3. To determine if self-referential measurement correlates positive with the actual emotional response.
4. To assess if BPD symptomatology correlates positively with the emotional response.

5. To investigate if self-rated emotional response does correlate with psychophysiological measurements of emotional response within and between groups.

Methods and analysis

Participants

In total 90 participants (30 BPD patients, 30 depressed patients, and 30 healthy control subjects) aged from 18-60 years will be recruited. To control for altered autonomic response all participants have to be free of severe, persistent neurological disorders (in particular, epilepsy, multiple sclerosis, stroke or neurodegenerative disease) and are not allowed to be currently medicated with antihistamines, neuroleptic medication, tranquilizers or beta blockers. Further, the BPD patients need to have a lifetime history of self-injury. Further exclusion criteria for the BPD patients are: psychotic disorders, current major depressive episode, acute suicidal crisis. The patients in the depressed control group need to have a depressive episode > 2weeks. The control groups will be matched to the BPS group for age and sex. The healthy control group has not to exhibit a current psychiatric disorder or history of self-injury.

Patient and public involvement

Patients were not involved in the development of the research question, outcome measures or study design.

Diagnostic procedure

Assessments of DSM-IV Personality Disorders (ADP-IV) (Doering et al., 2007; Schotte & De Doncker, 1994) and the Borderline Symptom Checklist (BSL-23) (Wolf et al., 2009) will be used to verify the diagnosis of BPD and to assess BPD symptoms. The structured clinical interview (SKID I,II) will be performed to assess psychiatric disorders (Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997).

To record the history and methods of self-injury, the Inventory of Statements about Self-Injury and the Self-Harm Behavior Questionnaire will be applied (Gutierrez, Osman, Barrios, & Kopper, 2001; Klonsky & Glenn, 2009). The general psychopathology will be recorded with the symptom checklist-90 (SCL-90) (Franke, 2002). Depressive symptoms will be self-rated with the Beck Depression Inventory (BDI) (Beck, Steer, & Brown, 1996). Since the study will assess the emotional processing of images, the current mood and stress of the participants could have an influence. Therefore, they will be asked how emotionally strained and charged they are at the moment before

and during testing on a Likert-scale ranging from 0-10. To check on the patient, a short break in the middle of the experiment is planned. Acute somatic and psychological dissociation will be assessed by the short version of the Dissociative State Scale (DSS) (Stiglmayr, Braakmann, Haaf, Stieglitz, & Bohus, 2003). Further, a demographic questionnaire, as well as the Edinburgh Handedness Inventory (Oldfield, 1971) will be applied.

Stimuli

Photographs and image processing will be made by a professional photographer. Three categories of objects and scenes for NSSI are planned to be photographed: objects that are frequently used for NSSI by BPD patients (self-injury objects; SIO), scenic presentation of usage shortly before the injury (SIO_{bi}), and scenic presentation during the usage of SIO (SIO_{dur}). SIO's will be selected based on the prevalence of usage decided from psychiatrists' expertise and on the existing literature (Brown et al., 2018; E David Klonsky, 2007; Jennifer Svaldi, Christina Dorn, Swantje Matthies, & Alexandra Philipsen, 2012). Actors that are instructed by the experimenters will play the mimicking of the usage of SIO's. Here, only the arms will be visible. Each image that involves body-parts will be acted by a man and a woman to prevent gender bias in the judgement (see Figure 2 for examples from EPSI for the three categories of objects and scenes).

Experimental Design

Participants will be asked to watch the images and to rate their current emotion on a scale of arousal, dominance, and valence. For this purpose, the self-assessment manikin (SAM) will be used (Margaret M Bradley & Peter J Lang, 1994). As control images to the SIO images, neutral objects (e.g., tools) will be shown (see Figure 1 for examples of neutral images). The neutral images will be taken from an existing and validated image database (Blechert, Meule, Busch, & Ohla, 2014). After half of the stimuli, a break will be done to check for the emotional status of the participants to assess and to prevent dissociations (Jaeger et al., 2017). Image presentation will be pseudorandomized across all categories. In order to prevent decomposition of the patients to the content of the stimuli, the patients will be monitored during the whole session by a therapist to intervene when necessary. In total 90 images will be shown (45 EPSI/ 45 neutral) each shown for 500ms followed by the judgement of the SAM.judgement of the SAM (see Figure 3 for the study design).

-Please insert Figure1-

Figure 1. *Examples of neutral pictures from food-pics: an image database for experimental research on eating and appetite*

-Please insert Figure2-

Figure 2. *Examples from EPSI for the three categories of objects and scenes for NSSI. From first in a row: objects that are frequently used for NSSI by BPD patients (self-injury objects; SIO), scenic presentation of usage shortly before the injury (SIO_{bi}), and scenic presentation during the usage of SIO (SIO_{dur}).*

Physiological Measurement

Autonomic nervous system

Assessment of the heart rate variability (HRV) is a valid and reliable indicator of the Autonomic Nervous System (ANS) and is considered as a transdiagnostic marker of psychopathology (Koenig et al., 2017; Wilson et al., 2016). Heart rate will be continuously recorded with an EC-12R rest-ecg. Three electrodes will be attached according to Einthoven's triangle plus a ground at the right lower limb (Einthoven, Fahr, & De Waart, 1913). HRV will be derived through a frequency domain analysis by taking the time-domain representation of the inter-beat-interval (IBI) and to convert it with a Fourier transformation to the frequency domain (Allen, Chambers, & Towers, 2007). Since we aim a recording of time at the length of the experiment, the ECG measurement can be considered as a short-term recording. Hence, the low-frequency band (LF; 0.04-0.15 Hz) and the high-frequency band (HF; 0.15-0.4 Hz) will be the frequencies of interest (Thayer, Hansen, & Johnsen, 2010).

Emotional face activation

The universal emotions happy, sad, angry, surprised, scared, disgusted and neutral as they were proposed by Ekman (Ekman & Keltner, 1970) will be measured with Noldus FaceReader software (Noldus Information Technology, www.noldus.com). The program detects facial expressions reliably and was successfully applied in numerous studies (Boerner, Chambers, McGrath, LoLordo, & Uher, 2017; Dalton, Jimenez, & Noussair, 2017). Throughout the whole session, the participants will be videotaped with a webcam. A frame-by-frame analysis will be done by the software. Over 500 key points of the participant's face are localized and compared to a database of annotated images. The intensity of the universal emotions is decoded on a scale from 0 to 1, where 0 means that the emotion is not present and 1 indicates an intensive emotional reaction. In addition to the universal emotions, the software also captures valence and arousal. Valence is calculated as the intensity of 'happy' minus the intensity of the negative expressions (angry, scared and disgusted) with the highest intensity. For arousal, the mean activation over the last 60 seconds of certain

muscle groups in the face is subtracted from the current muscle activation. The mean of the five highest values results in a value of arousal.

To prevent that the software has a bias towards certain expressions a calibration will be done with a neutral look of each participant.

-Please insert Figure3-

Figure 3. *Study design.*

Statistical analysis

Stimulus Validation

Interrater reliability will be assessed with Krippendorff's alpha. The advantage over other statistical methods to assess interrater reliability is that Krippendorff's alpha allows more than two raters (unlike Cohen's Kappa) and also can handle missing data points (unlike Fleiss Kappa) (Zapf, Castell, Morawietz, & Karch, 2016). The assumption of Krippendorff's alpha is based on the observed disagreement corrected for disagreement by chance, which is calculable to a range of -1 to 1, where 1 illustrates perfect agreement, 0 means no agreement beyond chance and negative values indicate inverse agreement (Krippendorff, 1970; Zapf et al., 2016). Bootstrapped confidence intervals will be used since the distribution is not known, the derivation of the correct standard error is not straight forward, and the type 1 error level is acceptable (McKenzie et al., 1996; Vanbelle & Albert, 2008; Zapf et al., 2016). Krippendorff's alpha will be computed for each SAM-dimension for each stimuli category.

Behavioral Data

If the data show normal distribution, a 2x3x4 between subjects analysis of variance (ANOVA) will be computed with the factors group, SAM-evaluation and stimuli category. Further, the questionnaire-scores will be correlated with the SAM-evaluations for each stimulus category. To assess gender bias, a linear regression will be performed to rule out possible performance differences.

Physiological Data

HRV

Group-wise comparisons of HRV will be computed with a 2x2x4 ANOVA with the factors group, frequencies and stimuli category.

Emotional Face Activation

Facial expressions will be evaluated group-wise for each of the six universal emotions and stimuli category, which results in a 2x4x6 ANOVA under the condition of normal distributed data. Besides t-testing the group difference in valence and arousal, a correlation will be calculated with the SAM dimensions of valence and arousal. This serves as a further measure of reliability of the participant's behavioral response with their physiological reaction to the stimuli.

Sample size justification

Using G*Power to estimate the effect size, based on a fixed effects ANOVA with 30 participants per group yield in a large effect size (0.62) with a power of 0.66 (Faul, Erdfelder, Lang, & Buchner, 2007). The size of the groups were derived from earlier studies that compares the affective reaction of BPS patients with healthy control while image watching (David Eddie & Marsha E Bates, 2017; Christina Sauer, Elisabeth A Arens, Malte Stopsack, Carsten Spitzer, & Sven Barnow, 2014).

Ethics and dissemination

The study will be conducted in accordance with the declaration of Helsinki in order to ensure the well-being and rights of the participants. The project has received ethical approval by the local medical ethics committee of the Carl-von-Ossietzky University of Oldenburg (registration: 2017-044). Written informed consent will be obtained from all participants. Participants will be able to withdraw from the study at any time without giving any reasons. During all measurement, medical professionals will be present. The study is registered at ClinicalTrials (URL) with the trial registration number: NCT03149926. Results of the main trial and each of the secondary endpoints will be submitted for publication in a peer-reviewed journal.

We used the SPIRIT checklist when writing our report (Chan et al., 2013)

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Authors´s contributions

KB, MS: study design, literature search, figures, writing

PS: study design, literature search, writing, supervision

CS: study design, supervision

AP: study design, literature search, writing, supervision

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Competing interests statement

KB, MS, PS, CS declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AP declares that she served on advisory boards, gave lectures, performed phase 3 studies, or received travel grants within the last 3 years from Eli Lilly and Co, Lundbeck, MEDICE Arzneimittel, Pütter GmbH and Co KG, Novartis, Servier, and Shire; and has authored books and articles on ADHD published by Elsevier, Hogrefe, Schattauer, Kohlhammer, Karger, and Springer.

We used the SPIRIT checklist when writing our report (Chan et al., 2013)

Figure 1. Examples of neutral pictures from food-pics: an image database for experimental research on eating and appetite

139x71mm (300 x 300 DPI)

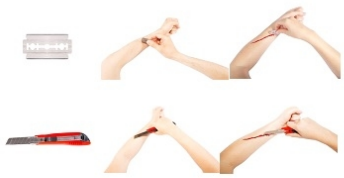

Figure 2. Examples from EPSI for the three categories of objects and scenes for NSSI. From first in a row: objects that are frequently used for NSSI by BPD patients (self-injury objects; SIO), scenic presentation of usage shortly before the injury (SIObi), and scenic presentation during the usage of SIO (SIOdur).

85x69mm (300 x 300 DPI)

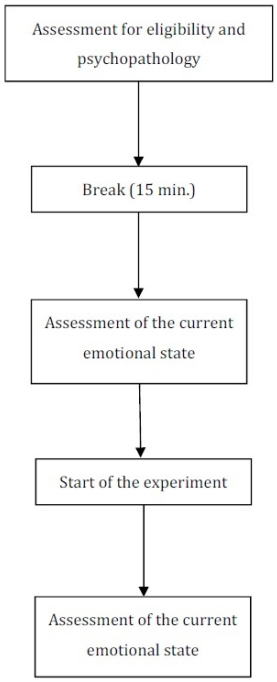

Figure 3. Study design.

92x71mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3, 15
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	n/a
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-8
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7-8
Objectives	#7	Specific objectives or hypotheses	8-9
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	9-10
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9
Interventions:	#11a	Interventions for each group with sufficient detail to allow	9-13

description		replication, including how and when they will be administered	
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9, 10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9, 10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8,11,12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9,14
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9 – 11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9-11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11-14
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	3
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	n/a
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	15
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Protocol article: Development and validation of an emotional picture set of self-injury (EPSI) for borderline personality disorder

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Keywords:	Borderline, Emotion regulation, Emotional stimuli, NSSI

Protocol article: Development and validation of an emotional picture set of self-injury (EPSI) for borderline personality disorder

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Abstract

Introduction: Borderline personality disorder (BPD) is a severe psychiatric disorder that is characterized by major problems in emotion regulation. Affected persons frequently engage in non-suicidal self-injury (NSSI) to regulate emotions. NSSI is associated with high emotionality in BPD patients and it can be expected that stimuli depicting scenes of NSSI elicit an emotional response distinctive for BPD. The current study protocol describes the development and validation of an emotional picture set of self-injury (EPSI) to advance future research on emotion regulation in BPD.

Methods and analysis: The current case-controlled experiment aims to develop and validate an emotional picture set relevant for BPD. Emotional response to EPSI as well as to a neutral picture set will be investigated in a sample of 30 BPD patients compared to 30 matched, healthy controls and to 30 matched depressive controls. Emotional response will be assessed by heart rate variability (HRV), facial expression and Self-Assessment Manikin (SAM).

Ethics and dissemination: Ethics approval was obtained by the medical ethics committee of the Carl-von-Ossietzky University of Oldenburg, Germany (registration: 2017-044). Results of the trial will be submitted for publication in a peer-reviewed journal.

Trial registration number: clinicaltrials.gov: NCT03149926

Keywords: Borderline, Emotion regulation, Emotional stimuli, NSSI

Strengths and limitations of this study

- Controlled study design to develop emotional stimuli relevant for BPD
- Emotional reaction is assessed by subjective as well as objective measurements
- Emotion evocation is limited to NSSI however other emotional trigger (e.g. social interaction) are not investigated
- Limited to BPD patients that actually engage in NSSI

Introduction

Borderline personality disorder (BPD) is a severe psychiatric disorder that is characterized by impairments in interpersonal, cognitive, and emotional functioning [1 2]. Pervasive problems in affect regulation have been identified as the central area of dysfunction in BPD. BPD even has been conceptualized as a disorder of the emotion regulation system [3]. Emotion dysregulation comprises high emotional vulnerability in conjunction with an inability to regulate emotions. Emotional vulnerability in individuals with BPD is characterized by high sensitivity to emotional stimuli, unusual emotional intensity and a slow return to emotional baseline (emotions are long-lasting). In addition, the identification, expression, and inhibition of emotions are impaired [3-5].

Not surprisingly, emotionally evocative material is commonly used to investigate BPD pathology. Previous studies have employed various emotional stimuli such as emotional facial expression [6 7], pleasant or unpleasant pictures [8 9], pictures and video clips depicting social interactions [10 11] or script-driven imagery of an act of self-injury [12]. However, research findings on emotion regulation in BPD to date are inconsistent in terms of evoking emotional responses in BPD patients [13 14]. While some studies did not find evidence for abnormal emotional responsiveness in BPD [9 15 16] others did [12 17 18]. One possible explanation for these contradictory results might be that the stimulus material was not specific enough to elicit an emotional response in persons with BPD. For example, in a recent study that investigated difference in emotional response and specificity of the presented stimuli, baseline emotional intensity and emotional reactivity in BPD patients were compared to healthy controls. Emotional response to six discrete emotion-eliciting film clips was evaluated by means of physiological and subjective reactions. Furthermore, the two groups were compared regarding their emotional reaction to films containing content associated with BPD (e.g. sexual abuse, emotional dependence, and abandonment/separation). Compared to healthy controls, persons with BPD did not show subjectively heightened reactivity to most of the discrete emotion-eliciting films but a significantly stronger emotional response to ‘‘BPD-specific content’’ films [18]. These findings suggest that measuring emotional responses that are characteristic for BPD only make sense in contexts that are psychologically challenging [9 13]. The actual emergence and intensity of emotions depend on an array of psychological characteristics of the person such as personality, learning experiences and cognition, the situational context but also on the type and intensity of the perceived stimulus [19]. Emotional stimuli that activate specific, self-relevant information seem to arouse a more intense emotional reaction than more general emotional stimuli [5 20]. Therefore, to elicit a distinctive and BPD-specific emotional response the stimulus material has to have a high

relevance for persons with BPD and has to trigger sensitivities distinct for BPD [5 9]. Such a triggering event could be the presentation of material used for non-suicidal self-injury (NSSI).

NSSI is associated with clinical and functional impairments and occurs in a variety of psychiatric disorders [21]. There is an ongoing scientific debate regarding the conceptualization and diagnostic organization of NSSI. The fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) presents Non-Suicidal Self-Injury Disorder (NSSID) as a separate nosological entity however as a condition that requires further investigation [21 22]. This shows that NSSI is not unique to BPD. However, there is a general consensus that NSSI is related to BPD and can be considered as a core symptom of the disorder [1 21]. NSSI is defined as the deliberate destruction of healthy body tissue that is not suicidal in nature. About 90% of patients with BPD do engage in NSSI [23]. NSSI typically includes repeated behaviors, such as skin cutting, banging or hitting, burning, scratching, and interfering with wound healing [24]. Emotion dysregulation is closely linked to NSSI in persons with BPD. According to the experiential avoidance model, NSSI is applied to reduce or remove aversive emotional experiences and might be maintained by negative reinforcement [25-27].

Empirical evidence suggests that NSSI is commonly performed as emotion regulation strategy. Self-injurers use NSSI to reduce unpleasant feelings, overcome dissociation, for self-punishment or for the reduction of aversive inner tension [28 29]. Typically, NSSI is preceded by high arousal of negative emotions whereas NSSI behavior is associated with a decrease in these emotions [29 30]. For example, a decrease in negative affect and arousal was observed in self-injurers who were asked to visualize cutting or to engage in another painful behavior whereas the performance of a non-NSSI-related task did not lead to a decrease [29]. In addition, seeing blood during NSSI seems to be an important aspect for many self-injurers. Glenn and Klonsky [31] investigated the role of seeing blood during NSSI in persons with a history of NSSI. Most participants (51.6%) reported seeing blood during NSSI was important. Furthermore, participants reported that seeing blood fulfilled multiple functions, such as to relieve tension (84.8%), to calm down (72.7%), to feel real (51.5%), to show the realness of NSSI (42.4%), to help focus (33.3%), and to show that NSSI has been performed correctly/deep enough (15.2%). A pilot study by Naoum, et al. [32] compared 20 female BPD patients and 20 healthy controls (HC) to investigate the effect of seeing blood during NSSI following stress and pain induction. The BPD patients showed a significantly stronger decrease in arousal than the HC group, however with no significant effects between blood and non-blood conditions. In addition, the urge for NSSI, significantly greater decreased in the blood condition in BPD patients. Seeing blood did not result in greater relief of tension, though.

Despite the connection of deficient emotion regulation and NSSI in BPD, yet no study is available that uses stimuli depicting different stages of NSSI to investigate whether the emotional reaction of BPD patients is gradually dependent on the stage of NSSI shown by the stimuli. A specified stimuli-database, validated in a BPD population for evoking emotional responses in BPD is lacking.

This Study

Although emotion dysregulation is recognized as a core symptom of BPD, current evidence is inconsistent and contradictory. This could be, at least partially, explained by the use of unsuitable and unspecific emotional stimulus material that does not tap into BPD-relevant themes. However, to improve and extend research on emotion regulation in BPD the availability of validated emotional stimuli that reliably elicit emotional reactions distinct for BPD is a necessary prerequisite.

This study aims to develop and validate an emotional picture set, EPSI (emotional picture set with scenes of self-injury), relevant for BPD. In a second step, the emotional reaction will be assessed by means of a self-report measurement as well as by a psychophysiological assessment of the emotional reaction in a sample of persons with BPD who engage in NSSI, in a depressive control group, and in a sample of matched healthy controls. Furthermore, participants are asked to indicate how strong the pictures relate to their person or biography. EPSI depicts objects frequently used for NSSI and shows the application of these objects at different stages of NSSI (objects only, pre-NSSI, NSSI, during-NSSI). As NSSI can be associated with different emotional reactions depending on the stage of NSSI, differences in the emotional reaction are expected for persons with BPD for the specific NSSI categories. In the pre-NSSI stage (preparing for NSSI), negative affect, arousal, and tension are expected to be strongest. When starting NSSI, negative affect, arousal, and tension might start to decrease. In the during-NSSI stage (successfully performed NSSI, seeing blood), an even stronger decrease of emotions and a sense of relief and relaxation is expected. It is hypothesized that the control groups show the opposite emotional reaction with lowest emotional response when seeing pictures of a pre-NSSI stage and strongest emotional response when watching during-NSSI pictures. Furthermore, BPD participants are expected to report higher self-reference regarding the pictures in comparison to the healthy controls.

To investigate if our database is BPD relevant, the evaluations of the NSSI images will be compared to neutral images and also to two different control groups. This study allows investigating to what extent EPSI can elicit an emotional response distinctive for persons with BPD and if the emotional response differs with regard to the stage of NSSI.

Objectives

Primary outcome variables are self-rated emotional reaction measured with the Self-Assessment-Manikin (SAM, [33]); psychophysiological parameters of emotional reaction will be assessed by heart rate variability (HRV) as indicator of autonomic nervous system (ANS) activity and analyses of facial expression as measured with Noldus FaceReader software (Noldus Information Technology, www.noldus.com). As a secondary outcome variable, self-reference of EPSI will be measured on a 5-point Likert-scale with the item 'How much do you see a relation to your own person/ to your biography?' from 1 (not at all) to 5 (very much) [18].

Primary objectives:

1. To develop a BPD-relevant stimulus set, an image database of NSSI will be created (EPSI).
2. To validate EPSI, the emotional reaction to EPSI will be compared to the emotional reaction to neutral stimuli within groups. Moreover, the emotional reaction to EPSI will be compared between patients with BPD, depressed patients, and healthy controls.

Secondary objectives:

1. To assess the extent, to which the emotional reaction to EPSI in persons with BPD who engage in NSSI is gradually dependent when seeing pre-NSSI, NSSI, and during NSSI pictures.
2. To investigate if persons with BPD who engage in NSSI rate EPSI as more self-referential than matched healthy controls and depressive controls.
3. To determine if self-referential measurement correlates positively with the actual emotional response.
4. To assess if BPD symptomatology correlates positively with the emotional response.
5. To investigate if self-rated emotional response does correlate with psychophysiological measurements of emotional response within and between groups.

Methods and analysis

Participants

In total 90 participants (30 BPD patients, 30 depressed patients, and 30 healthy control subjects) aged from 18-60 years will be recruited. To control for altered autonomic response all participants have to be free of severe, persistent neurological disorders (in particular, epilepsy, multiple sclerosis, stroke or neurodegenerative disease) and are not allowed to be currently medicated with

antihistamines, neuroleptic medication, tranquilizers or beta blockers. Further, the BPD patients need to have a lifetime history of self-injury. Exclusion criteria for the BPD patients are psychotic disorders, current major depressive episode, and acute suicidal crisis. The patients in the depressed control group need to suffer from current major depressive episode (depressive symptoms for at least 2 weeks). Depressive patients who also met diagnostic criteria for a psychotic disorder will be excluded. The healthy control group must not exhibit a current psychiatric disorder or history of self-injury. Additional exclusion criteria for both control groups are attempted suicide or current suicide ideation. The control groups will be matched to the BPD group for age and sex.

Patient and public involvement

Patients were not involved in the development of the research question, outcome measures or study design.

Diagnostic procedure

Assessments of DSM-IV Personality Disorders (ADP-IV) [34 35] and the Borderline Symptom Checklist (BSL-23) [36] will be used to verify the diagnosis of BPD and to assess BPD symptoms. The structured clinical interview (SCID I,II) will be performed to assess psychiatric disorders [37].

To record the history and methods of self-injury, the Inventory of Statements about Self-Injury (ISAS) and the Self-Harm Behavior Questionnaire (SHQ) will be applied [38 39]. Any outcome above zero ,that means NSSI has been performed, on the ISAS or SHQ will be an exclusion criterion The general psychopathology will be recorded with the symptom checklist-90 (SCL-90) [40]. Depressive symptoms will be self-rated with the Beck Depression Inventory (BDI) [41]. Since the study will assess the emotional processing of images, the current mood and stress of the participants could have an influence. Therefore, they will be asked how emotionally strained and charged they are at the moment before and during testing on a Likert-scale ranging from 0-10. To check on the patient, a short break in the middle of the experiment is planned. Acute somatic and psychological dissociation will be assessed by the short version of the Dissociative State Scale (DSS) [42]. Further, a demographic questionnaire, as well as the Edinburgh Handedness Inventory [43] will be applied.

Stimuli

Photographs and image processing will be made by a professional photographer. Three categories of objects and scenes for NSSI are planned to be photographed: objects that are frequently used for NSSI by BPD patients (self-injury objects; SIO), scenic presentation of usage shortly before the injury (SIO_{bi}), and scenic presentation during the usage of SIO (SIO_{dur}). SIOs will be selected based on the

prevalence of usage decided from psychiatrists' expertise and on the existing literature [44-46]. Actors that are instructed by the experimenters will play the mimicking of the usage of SIOs. Here, only the arms will be visible. Each image that involves body-parts will be acted by a man and a woman to prevent gender bias in the judgment (see Figure 1 for examples from EPSI for the three categories of objects and scenes).

Experimental Design

Participants will be asked to watch the images and to rate their current emotion on a scale of arousal, dominance, and valence. For this purpose, the Self-Assessment Manikin (SAM) will be used [47]. As control images to the SIO images, neutral objects (e.g., tools) will be shown (see Figure 2 for examples of neutral images). The neutral images will be taken from an existing and validated image database [48]. After half of the stimuli, a break will be done to check for the emotional status of the participants to assess and to prevent dissociations [49]. Image presentation and SAM rating-screens will be pseudorandomized across all categories. In order to prevent decomposition of the patients to the content of the stimuli, the patients will be monitored during the whole session by a therapist to intervene when necessary. In total 90 images will be shown (45 EPSI/ 45 neutral) each shown for 500 ms followed by the judgment of the SAM (see Figure 3 for the study design). At the end of the experiment, participants will perform a self-reference rating on all EPSI picture. This will be measured by means of a 5-point scale with anchors: 1="Not at all related to me" s and 5= "Definitely related to me". See table 1 for study timeline flow.

-Please insert Figure 1-

Figure 1. *Examples from EPSI for the three categories of objects and scenes for NSSI. From first in a row: objects that are frequently used for NSSI by BPD patients (self-injury objects; SIO), scenic presentation of usage shortly before the injury (SIO_{bi}), and scenic presentation during the usage of SIO (SIO_{dur}).*

-Please insert Figure 2-

Figure 2. *Examples of neutral pictures from food-pics: an image database for experimental research on eating and appetite*

Physiological Measurement

Autonomic nervous system

Assessment of the heart rate variability (HRV) is a valid and reliable indicator of the autonomic nervous system (ANS) and is considered as a transdiagnostic marker of psychopathology [50 51]. Heart rate will be continuously recorded with an EC-12R PC-based resting ECG system (Labtech, Debrecen, Hungary). Three electrodes will be attached according to Einthoven's triangle plus a ground at the right lower limb [52]. HRV will be derived through a frequency domain analysis by taking the time-domain representation of the inter-beat-interval (IBI) and to convert it with a Fourier transformation to the frequency domain [53]. Since we aim a recording of time at the length of the experiment, the ECG measurement can be considered as a short-term recording. Hence, the low-frequency band (LF; 0.04-0.15 Hz) and the high-frequency band (HF; 0.15-0.4 Hz) will be the frequencies of interest [54]. Processing of the HRV-data will be done with the Kubios HRV software (www.kubios.com) [55]. A threshold-based artifact correction algorithm, as it is implemented in the Kubios software will be performed. To separate ectopic and misplaced beats from the normal sinus rhythm, the automatic artifact correction algorithm will be used[55]. Further, heart rate reactivity will be calculated.

Emotional face activation

The universal emotions happy, sad, angry, surprised, scared, disgusted, and neutral as proposed by Ekman [56] will be measured with Noldus FaceReader software (Noldus Information Technology, www.noldus.com). The program detects facial expressions reliably and was successfully applied in numerous studies [57 58]. Throughout the whole session, the participants will be videotaped with a webcam. A frame-by-frame analysis will be done by the software. Over 500 key points of the participant's face are localized and compared to a database of annotated images. The intensity of the universal emotions is decoded on a scale from 0 to 1, where 0 means that the emotion is not present and 1 indicates an intensive emotional reaction. In addition to the universal emotions, the software also captures valence and arousal. Valence is calculated as the intensity of 'happy' minus the intensity of the negative expressions (angry, scared, and disgusted) with the highest intensity. For arousal, the mean activation over the last 60 seconds of certain muscle groups in the face is subtracted from the current muscle activation. The mean of the five highest values results in a value of arousal.

To prevent a bias towards certain expressions a calibration will be done with a neutral look for each participant.

-Please insert Figure3-

Figure 3. A) *Study design. B) Experimental paradigm; NSSI=non-suicidal self-injury; SAM I/II/III=Self-Assessment Manikin (Dominance, Arousal, and Valence) presented pseudorandomized*

Statistical analysis

Stimulus Validation

Interrater reliability will be assessed with Krippendorff's alpha. The advantage over other statistical methods to assess interrater reliability is that Krippendorff's alpha allows more than two raters (unlike Cohen's Kappa) and also can handle missing data points (unlike Fleiss Kappa) [59]. The assumption of Krippendorff's alpha is based on the observed disagreement corrected for disagreement by chance, which is calculable to a range of -1 to 1, where 1 illustrates perfect agreement, 0 means no agreement beyond chance, and negative values indicate inverse agreement [59 60]. Bootstrapped confidence intervals will be used since the distribution is not known, the derivation of the correct standard error is not straightforward, and the type 1 error level is acceptable [59 61 62]. Krippendorff's alpha will be computed for each SAM-dimension for each stimuli category.

Behavioral Data

If the data show normal distribution, a 2x3x4 between-subjects analysis of variance (ANOVA) will be computed with the factors group, SAM-evaluation, and stimulus category. Further, the questionnaire scores will be correlated with the SAM-evaluations for each stimulus category. To assess gender bias, a linear regression will be performed to rule out possible performance differences.

Physiological Data

HRV

Group-wise comparisons of HRV will be computed with a 2x2x4 ANOVA with the factors group, frequencies, and stimulus category.

Emotional Face Activation

Facial expressions will be evaluated group-wise for each of the six universal emotions and stimulus categories, which results in a 2x4x6 ANOVA under the assumption of normally distributed data. Besides t-testing the group difference in valence and arousal, a correlation will be calculated with the SAM dimensions of valence and arousal. This serves as a further measure of the reliability of the participants' behavioral response with their physiological reaction to the stimuli.

Sample size justification

Based on calculations with G*Power, a fixed effects ANOVA with 30 participants per group will yield a large effect size (0.62) with a power of 0.66.[63]. The size of the groups was derived from earlier studies comparing the affective reaction of BPD patients with healthy controls while watching images [64 65].

Table 1 Study timeline flow

Months	**1st year**				**2st year**				**3rd year**			
	1	4	7	10	13	16	19	22	25	28	31	34
Study preparation	X	X										
Recruitment	X	X	X									
Clinical conduct			X		X	X						
Database clearing					X	X						
Data analysis, publication					X	X	X	X	X	X	X	X

Ethics and dissemination

The study will be conducted in accordance with the declaration of Helsinki in order to ensure the well-being and rights of the participants. The project has received ethical approval by the local medical ethics committee of the Carl-von-Ossietzky University of Oldenburg (registration: 2017-044). Written informed consent will be obtained from all participants. Participants will be able to withdraw from the study at any time without giving any reasons. During all measurement, medical professionals will be present. The study is registered at ClinicalTrials (URL) with the trial registration number: NCT03149926. Results of the main trial and each of the secondary endpoints will be submitted for publication in a peer-reviewed journal.

We used the SPIRIT checklist when writing our report [66]

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Authors´s contributions

KB, MS: study design, literature search, figures, writing

PS: study design, literature search, writing, supervision

CS: study design, supervision

AP: study design, literature search, writing, supervision

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KB, MS, PS, CS declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AP declares that she served on advisory boards, gave lectures, performed phase 3 studies, or received travel grants within the last 3 years from Eli Lilly and Co, Lundbeck, MEDICE Arzneimittel, Pütter GmbH and Co KG, Novartis, Servier, and Shire; and has authored books and articles on ADHD published by Elsevier, Hogrefe, Schattauer, Kohlhammer, Karger, and Springer.

We used the SPIRIT checklist when writing our report [66]

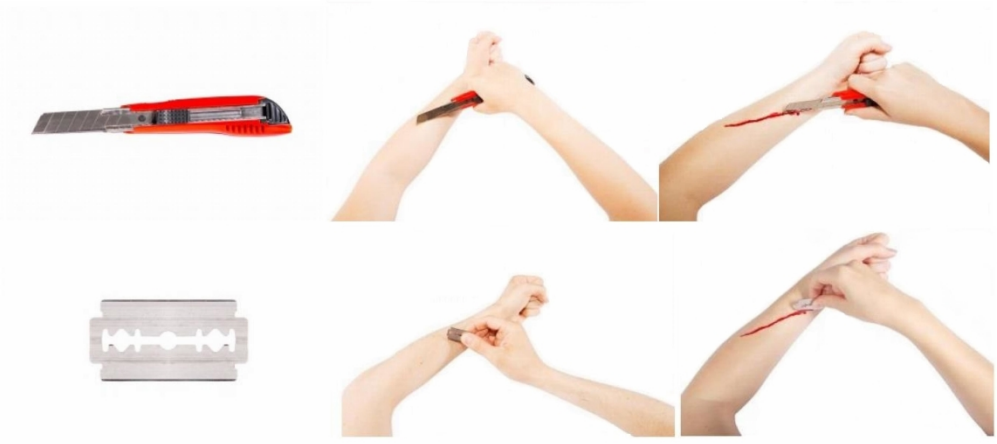

Figure 1. Examples from EPSI for the three categories of objects and scenes for NSSI. From first in a row: objects that are frequently used for NSSI by BPD patients (self-injury objects; SIO), scenic presentation of usage shortly before the injury (SIObi), and scenic presentation during the usage of SIO (SIOdur).

312x154mm (300 x 300 DPI)

Figure 2. Examples of neutral pictures from food-pics: an image database for experimental research on eating and appetite

311x93mm (300 x 300 DPI)

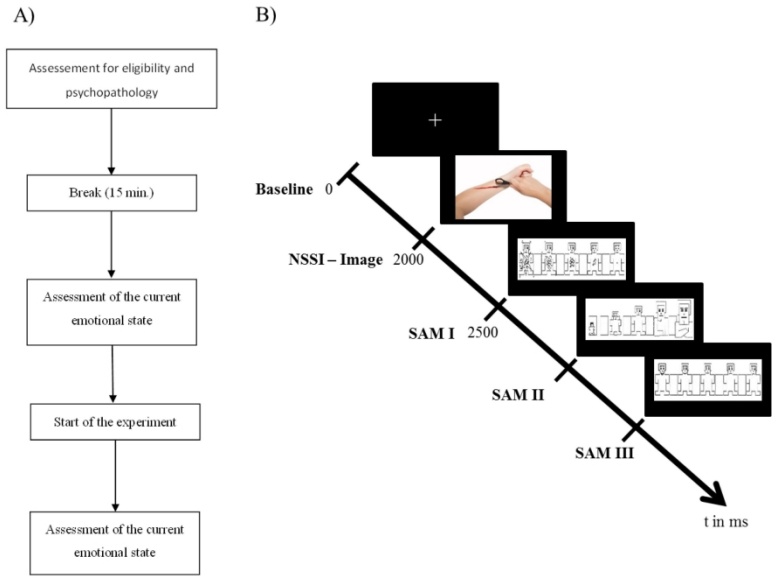

Figure 3. A) Study design. B) Experimental paradigm; NSSI=non-suicidal self-injury; SAM I/II/III=Self-Assessment Manikin (Dominance, Arousal, and Valence) presented pseudorandomized

311x196mm (300 x 300 DPI)

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Development and validation of an emotional picture set of self-injury (EPSI) for borderline personality disorder: protocol for a validation study

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Development and validation of an emotional picture set of self-injury (EPSI) for borderline personality disorder: protocol for a validation study

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Abstract

Introduction: Borderline personality disorder (BPD) is a severe psychiatric disorder that is characterized by major problems in emotion regulation. Affected persons frequently engage in non-suicidal self-injury (NSSI) to regulate emotions. NSSI is associated with high emotionality in BPD patients and it can be expected that stimuli depicting scenes of NSSI elicit an emotional response indicative of BPD. The present study protocol describes the development and validation of an emotional picture set of self-injury (EPSI) to advance future research on emotion regulation in BPD.

Methods and analysis: The present validation study aims to develop and validate an emotional picture set relevant for BPD. Emotional responses to EPSI as well as to a neutral picture set will be investigated in a sample of 30 BPD patients compared to 30 matched, healthy controls and to 30 matched depressive controls. Emotional responses will be assessed by heart rate variability (HRV), facial expression and Self-Assessment Manikin (SAM).

Ethics and dissemination: Ethics approval was obtained by the medical ethics committee of the Carl-von-Ossietzky University of Oldenburg, Germany (registration: 2017-044). Results of the trial will be submitted for publication in a peer-reviewed journal.

Trial registration number: clinicaltrials.gov: NCT03149926

Keywords: Borderline, Emotion regulation, Emotional stimuli, NSSI

Strengths and limitations of this study

- Controlled study design to develop emotional stimuli relevant for BPD
- Emotional reaction is assessed by subjective as well as objective measurements
- Emotion evocation is limited to NSSI however other emotional trigger (e.g. social interaction) are not investigated
- Limited to BPD patients that actually engage in NSSI

Introduction

Borderline personality disorder (BPD) is a severe psychiatric disorder that is characterized by impairments in interpersonal, cognitive and emotional functioning [1 2]. Pervasive problems of affect regulation have been identified as the central dysfunction in BPD and it has been conceptualized as a disorder of the emotion regulation system [3]. Emotion dysregulation comprises high emotional vulnerability in conjunction with an inability to regulate emotions. Emotional vulnerability in individuals with BPD is characterized by high sensitivity to emotional stimuli, unusual emotional intensity and a slow return to emotional baseline (emotions are long-lasting). In addition, the identification, expression and inhibition of emotions are impaired [3-5].

Not surprisingly, emotionally evocative material is commonly used to investigate BPD pathology. Previous studies have employed various emotional stimuli such as emotional facial expression [6 7], pleasant or unpleasant pictures [8 9], pictures and video clips depicting social interactions [10 11], or script-driven imagery of a self-injurious act [12]. However, extant research utilizing such emotionally evocative materials are inconsistent in their ability to provoke emotional responses in BPD patients [13 14]. While some studies did not find evidence for abnormal emotional responsiveness in BPD [9 15 16] others did [12 17 18]. One possible explanation for these contradictory results might be that the stimulus material was not specific enough to elicit an emotional response in participants with BPD. For example, a recent study investigated differences in emotional response and specificity of the presented stimuli, as well as baseline emotional intensity and emotional reactivity in BPD patients, compared to healthy controls. Emotional response to six discrete emotion-eliciting film clips was evaluated by measuring physiological and subjective reactions. Furthermore, the two groups were compared regarding their emotional reaction to films with BPD-specific content (e.g. sexual abuse, emotional dependence and abandonment/separation). Compared to healthy controls, participants with BPD showed a significantly stronger emotional response to 'BPD-specific content' films [18], compared to films with non-BPD-specific emotional content. These findings suggest that measuring emotional responses characteristic of BPD only make sense in contexts that are psychologically challenging [9 13]. The actual emergence and intensity of emotions depend on an array of psychological characteristics such as personality, learning experiences and cognition, the situational context, but also on the type and intensity of the perceived stimulus [19]. Emotional stimuli that activate specific, self-relevant information seem to arouse a more intense emotional reaction than more general emotional stimuli [5 20]. Therefore, to elicit a distinctive and BPD-specific emotional response, the stimulus material needs to have a high relevance for persons with BPD and needs to trigger

sensitivities that relate to BPD [5 9]. Such a BPD specific event could include the presentation of material used for non-suicidal self-injury (NSSI).

NSSI is associated with clinical and functional impairments and occurs in a variety of psychiatric disorders [21]. There is an ongoing scientific debate regarding the conceptualization and diagnostic organization of NSSI. The fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) presents Non-Suicidal Self-Injury Disorder (NSSID) as a separate nosological entity, but only as a condition that still requires further investigation [21 22]. Thus, NSSI is not unique to BPD. Nevertheless, there is a general consensus that NSSI is related to BPD and is considered to be a core symptom of the disorder [1 21]. NSSI is defined as a deliberate, albeit non-suicidal destruction of healthy body tissue, in which approximately 90% of BPD patients partake [23]. NSSI typically includes repeated behaviors, such as skin cutting, banging or hitting, burning, scratching and interfering with wound healing [24]. Further, emotion dysregulation is closely related to NSSI in persons with BPD. According to the experiential avoidance model, NSSI is applied to reduce or remove aversive emotional experiences and might be maintained by negative reinforcement [25-27].

Empirical evidence suggests that NSSI is commonly performed as an emotion regulation strategy. Self-injurers use NSSI to reduce unpleasant feelings, overcome dissociation, for self-punishment or for the reduction of aversive inner tension [28 29]. Typically, NSSI is preceded by high arousal of negative emotions, NSSI behavior is then initiated to decrease these emotions [29 30]. For example, a decrease in negative affect and arousal was observed in self-injurers who were asked to visualize cutting or to engage in another painful behavior, whereas the performance of a non-NSSI-related task did not lead to a decrease [29]. In addition, seeing blood during NSSI seems to be an important aspect for many self-injurers. Glenn and Klonsky [31] investigated the role of seeing blood during NSSI in persons with a history of NSSI. Most participants (51.6%) reported that seeing blood during NSSI was important. Furthermore, participants reported that seeing blood fulfilled multiple functions, such as to relieve tension (84.8%), to calm down (72.7%), to feel real (51.5%), to show the realness of NSSI (42.4%), to help focus (33.3%) and to show that NSSI has been performed correctly/deep enough (15.2%). A pilot study by Naoum, et al. [32] compared 20 female BPD patients and 20 healthy controls (HC) to investigate the effect of seeing blood during NSSI following stress and pain induction. The BPD patients demonstrated a significantly stronger decrease in arousal compared to the HC group however, with no significant differences between blood and non-blood conditions. In addition, the urge for NSSI was associated with a significantly greater decrease in arousal in the blood condition in BPD patients. Yet, seeing blood did not result in greater relief of tension.

Despite the connection between emotion regulation deficits and NSSI in BPD, there are currently no studies utilizing stimuli depicting the varying stages of NSSI. Doing so would help investigate whether emotional reactions in BPD patients gradually depends on the stage of NSSI presented by the stimuli. Thus, a specified stimuli-database, validated in a BPD population for evoking emotional responses in BPD is lacking.

This Study

Although emotion dysregulation is recognized as a core symptom of BPD, current evidence is inconsistent and contradictory. This could be explained, at least partially, by the use of unsuitable and unspecific emotional stimuli that do not tap into BPD-relevant themes. However, to improve and extend research on emotion regulation in BPD, the availability of validated emotional stimuli, that reliably elicit emotional reactions specifically for BPD, is a necessary prerequisite.

This study aims to develop and validate an emotional picture set, EPSI (emotional picture set with scenes of self-injury), relevant for BPD. In a second step, emotional reactions will be assessed by means of a self-report measurement, as well as by a psychophysiological assessment of emotional reactions in participants with BPD who engage in NSSI, in a depressive control group and in a sample of matched healthy controls. Furthermore, participants are asked to indicate how strong the pictures relate to their person or biography. EPSI depicts objects frequently used for NSSI and shows the application of these objects at different stages of NSSI (objects only, pre-NSSI and during-NSSI). As NSSI can be associated with different emotional reactions depending on the stage of NSSI, differences in the emotional reactions are expected for participants with BPD and their respective NSSI stage. In the pre-NSSI stage (preparing for NSSI), negative affect, arousal and tension are expected to be strongest. As NSSI behavior begins, negative affect, arousal and tension might start to decrease. In the during-NSSI stage (successfully performed NSSI i.e. seeing blood), an even stronger decrease of emotions and a sense of relief and relaxation is expected. We predict that the control groups will show emotional reactions opposite that of BPD, that is, the control groups are expected to show low emotional responses when seeing pictures of NSSI objects and pictures of the pre-NSSI stage; they will show strong responses when watching pictures of the during-NSSI stage. Lastly, BPD participants are expected to report higher self-referencing in response to the pictures when compared to controls.

To investigate whether our database is BPD relevant, evaluations of the NSSI images will be compared with neutral images and with two separate control groups. In this way, the present study

will investigate to what extent EPSI can elicit an emotional response specifically for persons with BPD and if the emotional response differs with regard to the stage of NSSI.

Objectives

The primary outcome variables include self-rated emotional reactions, as measured by the Self-Assessment-Manikin (SAM) [33]; psychophysiological parameters of emotional reactions will be assessed using heart rate variability (HRV), as an indicator of autonomic nervous system (ANS) activity. Finally, facial expressions will be analyzed and measured with the Noldus FaceReader software (Noldus Information Technology, www.noldus.com). As a secondary outcome variable, self-reference of EPSI will be measured on a 5-point Likert-scale, using the item 'How much do you see a relation to your own person/to your biography?' from 1 (not at all) to 5 (very much) [18].

Primary objectives:

1. An NSSI image database will be created (EPSI) to develop a BPD-relevant stimulus set.
2. A within-groups comparison of emotional reactions to EPSI and neutral stimuli will be conducted to validate EPSI. Moreover, the emotional reactions to EPSI will be compared amongst patients with BPD, depressed patients and healthy controls.

Secondary objectives:

1. To assess how emotional reactions in participants with BPD, who engage in NSSI, gradually depend on seeing NSSI objects, pre-NSSI pictures and during NSSI pictures.
2. To investigate if participants with BPD who engage in NSSI rate EPSI as more self-referential than matched healthy controls and depressive controls.
3. To determine if self-referential measurement correlates positively with the actual emotional response.
4. To assess if BPD symptomatology correlates positively with emotional responses.
5. To investigate if self-rated emotional responses correlates with psychophysiological measurements of emotional responses within and between groups.

Methods and analysis

Participants

In total, 90 participants (30 BPD patients, 30 depressed patients and 30 healthy control subjects) of18-60 years of age will be recruited. To control for altered autonomic responses, all participants

must be free of severe and persistent neurological disorders (in particular, epilepsy, multiple sclerosis, stroke or neurodegenerative diseases). Participants are not allowed to be currently medicated with antihistamines, neuroleptic medication, tranquilizers or beta blockers. Further, the BPD patients must have a lifetime history of self-injury. Exclusion criteria for the BPD patients include psychotic disorders, current major depressive episode and acute suicidal crisis. Patients in the depressed control group need to have a current major depressive episode (depressive symptoms for at least 2 weeks). Depressive patients who also meet diagnostic criteria for a psychotic disorder will be excluded. The healthy control group must not exhibit a current psychiatric disorder or history of self-injury. Additional exclusion criteria for both control groups include attempted suicide or current suicidal ideation. Control groups will be matched to the BPD group on age and sex.

Patient and public involvement

Patients were not involved in the development of the research question, outcome measures or study design.

Diagnostic procedure

Assessments of DSM-IV Personality Disorders (ADP-IV) [34 35] and the Borderline Symptom Checklist (BSL-23) [36] will be used to verify the diagnosis of BPD and to assess BPD symptoms. The structured clinical interview (SCID I,II) will be performed to assess psychiatric disorders [37]. Further, a demographic questionnaire , as well as the Edinburgh Handedness Inventory [38], will be applied.

To record the history and methods of self-injury, the Inventory of Statements about Self-Injury (ISAS) and the Self-Harm Behavior Questionnaire (SHQ) will be applied [39 40]. Any outcome above zero (meaning that NSSI has been performed) on the ISAS or SHQ will be an exclusion criterion. General psychopathology will be recorded with the symptom checklist-90 (SCL-90) [41]. Depressive symptoms will be self-rated with the Beck Depression Inventory (BDI) [42]. Since the study will assess the emotional processing of images, the current mood and stress of the participants could have an influence. Therefore, they will be asked how emotionally strained and charged they are at the moment before and during testing, using a Likert-scale ranging from 0-10. A short break is planned in the middle of the experiment to check on the patients' psychological distress. Acute somatic and psychological dissociation will be assessed via the short version of the Dissociative State Scale (DSS) [43].

Stimuli

A professional photographer will photograph and process three NSSI related object and scene categories . These will include objects that are frequently used for NSSI by BPD patients (self-injury objects; SIO), scenic presentation of SIO use shortly before the injury (SIO_{bi}) and scenic presentation during SIO use (SIO_{dur}). SIOs will be selected based on use frequency, psychiatrists' expertise, and on the existing literature [44-46]. Actors will be instructed by experimenters to mimic SIO use; only their arms will be visible. Each image involving body-parts will be portrayed by a man and woman, to prevent gender-biased judgment (see Figure 1 for examples from EPSI for the three categories of objects and scenes).

Experimental Design

Participants will be asked to watch the images and to rate their current emotion on scales of arousal, dominance and valence, for which the Self-Assessment Manikin (SAM) will be used [47]. In addition, neutral objects will be displayed to provide control images (e.g., towels, books; see Figure 2 for examples of neutral images), which will be taken from an existing and validated database [48]. A break will be included half way through the stimulus presentation, to assess participants' emotional status and to prevent dissociations [49]. Image presentation and SAM rating-screens will be pseudorandomized across all categories. Medical professionals will be monitoring the participants to prevent overstraining and to intervene if necessary. In total, 90 images will be shown (45 EPSI/ 45 neutral), each for 500 ms, followed by the SAM evaluation (see Figure 3 for the study design). At the end of the experiment, participants will perform a self-reference rating on all EPSI picture, using a 5-point scale with anchors: 1='Not at all related to me' and 5='Definitely related to me'. See table 1 for study timeline flow.

-Please insert Figure 1-

Figure 1. *Examples from EPSI for the three categories of objects and scenes for NSSI. From first in a row: objects that are frequently used for NSSI by BPD patients (self-injury objects; SIO), scenic presentation of usage shortly before the injury (SIO_{bi}) and scenic presentation during the usage of SIO (SIO_{dur}).*

-Please insert Figure 2-

Figure 2. *Examples of neutral pictures from food-pics: an image database for experimental research on eating and appetite*

Physiological Measurement

Autonomic nervous system

Heart rate variability (HRV) is a valid and reliable indicator of autonomic nervous system (ANS) activity, and is a transdiagnostic marker of psychopathology [50] [51]. Heart rate will be recorded continuously with an EC-12R PC-based resting ECG system (Labtech, Debrecen, Hungary). Three electrodes will be attached according to Einthoven's triangle and a ground at the right lower limb [52]. To derive HRV, a frequency domain analysis will be conducted by taking a Fourier transformed time-domain representation of the inter-beat-interval (IBI)[53]. Since we plan to record task-concurrent HR, the low (LF; 0.04-0.15 Hz) and high (HF; 0.15-0.4 Hz) frequency bands will be of particular interest, [54]. The HRV-data will be processed with the Kubios HRV software (www.kubios.com) [55]. A threshold-based artifact correction algorithm, as it is implemented in the Kubios software, will be performed. To separate ectopic and misplaced beats from the normal sinus rhythm, the automatic artifact correction algorithm will be used[55]. Further, heart rate reactivity will be calculated.

Emotional face activation

The universal emotions of happy, sad, angry, surprised, scared, disgusted, and neutral, as proposed by Ekman [56], will be measured with Noldus FaceReader software (Noldus Information Technology, www.noldus.com). The program reliably detects facial expressions and was successfully applied in numerous studies [57] [58]. Participants will be videotaped with a webcam throughout the session, using a frame-by-frame analysis during which 500+ key points of the participant's face will be localized and compared to a database of annotated images. The intensity of the universal emotions is then decoded on a scale from 0 to 1, where 0 indicates an absent emotion and 1 an intense emotional reaction. In addition to the universal emotions, the software also captures valence and arousal. Valence is calculated by subtracting the intensity of negative expressions (angry, scared and disgusted) from the intensity of 'happy' expressions. Arousal is calculated by subtracting the mean activation of specific facial muscle groups, occurring over the last 60 seconds, from current muscle activation. The mean of the five highest values then yields the value of arousal.

To prevent biased responses, each session will be calibrated with a neutral stimulus per participant.

-Please insert Figure3-

Figure 3. A) *Study design. B) Experimental paradigm; NSSI=non-suicidal self-injury; SAM I/II/III=Self-Assessment Manikin (dominance, arousal and valence) presented pseudorandomized*

Statistical analysis

Stimulus Validation

Interrater reliability will be assessed with Krippendorff's alpha. The advantage of this method over competing methods is that Krippendorff's alpha allows for more than two raters (unlike Cohen's Kappa) and can handle missing data points (unlike Fleiss Kappa) [59]. The assumption of Krippendorff's alpha is based on the observed disagreement corrected for disagreement by chance, which is calculable within a range of -1 to 1, where 1 illustrates perfect agreement, 0 no agreement beyond chance and negative values indicate inverse agreement [59 60]. Bootstrapped confidence intervals will be used since the distribution is not known, the derivation of the correct standard error is not straightforward and the type 1 error level is acceptable [59 61 62]. Krippendorff's alpha will be computed for each SAM-dimension, for each stimuli category.

Behavioral Data

If the data show a normal distribution, a 2x3x4 between-subjects analysis of variance (ANOVA) will be computed with the factors group, SAM-evaluation and stimulus category. Further, the questionnaire scores will be correlated with the SAM-evaluations for each stimulus category. To assess gender bias, a linear regression will be performed to rule out possible performance differences.

Physiological Data

HRV

Group-wise comparisons of HRV will be computed with a 2x2x4 ANOVA with the factors group, frequencies and stimulus category.

Emotional Face Activation

Facial expressions will be evaluated group-wise for each of the six universal emotions and stimulus categories, which results in a 2x4x6 ANOVA under the assumption of normally distributed data. Besides t-testing the group difference in valence and arousal, a correlation will be calculated with the SAM dimensions of valence and arousal. This serves as a further measure of the reliability of the participants' behavioral response with their physiological reaction to the stimuli.

Sample size justification

Based on calculations with G*Power, a fixed effects ANOVA with 30 participants per group will yield a large effect size (0.62) with a power of 0.66[63]. The size of the groups was derived from earlier studies comparing the affective reaction of BPD patients with healthy controls while watching images [64 65].

Table 1 Study timeline flow

Months	**1st year**				**2st year**				**3rd year**			
	1	4	7	10	13	16	19	22	25	28	31	34
Study preparation	X	X										
Recruitment	X	X	X									
Clinical conduct			X		X	X						
Database clearing					X	X						
Data analysis, publication					X	X	X	X	X	X	X	X

Ethics and dissemination

The study will be conducted in accordance with the declaration of Helsinki in order to ensure the well-being and rights of the participants. The project has received ethical approval by the local medical ethics committee of the Carl-von-Ossietzky University of Oldenburg (registration: 2017-044). Written informed consent will be obtained from all participants. Participants will be able to withdraw from the study at any time without giving any reasons. Medical professionals will be present at all times during the experiment. The study is registered at ClinicalTrials (URL), with the trial registration number: NCT03149926. Results of the main trial and each of the secondary endpoints will be submitted for publication in a peer-reviewed journal.

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Authors´s contributions

KB, MS: study design, literature search, figures, writing

PS: study design, literature search, writing, supervision

CS: study design, supervision

AP: study design, literature search, writing, supervision

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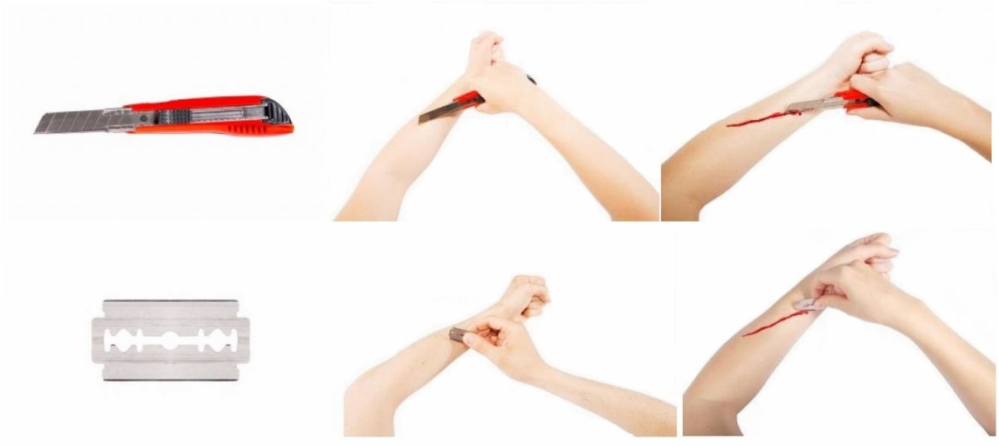

Figure 1. Examples from EPSI for the three categories of objects and scenes for NSSI. From first in a row: objects that are frequently used for NSSI by BPD patients (self-injury objects; SIO), scenic presentation of usage shortly before the injury (SIObi), and scenic presentation during the usage of SIO (SIOdur).

312x154mm (300 x 300 DPI)

Figure 2. Examples of neutral pictures from food-pics: an image database for experimental research on eating and appetite

311x93mm (300 x 300 DPI)

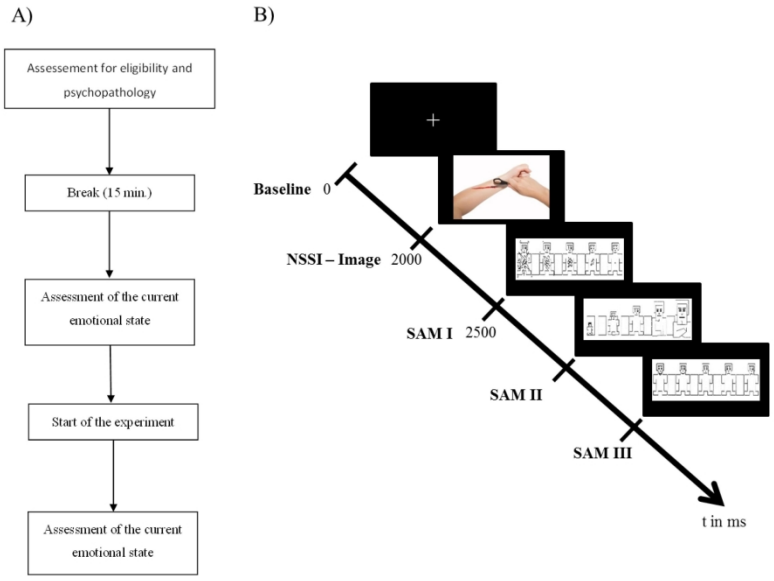

Figure 3. A) Study design. B) Experimental paradigm; NSSI=non-suicidal self-injury; SAM I/II/III=Self-Assessment Manikin (Dominance, Arousal, and Valence) presented pseudorandomized

311x196mm (300 x 300 DPI)