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

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48 **Abstract**

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

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

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

64 **Trial registration number:** [clinicaltrials.gov: NCT03149926](https://clinicaltrials.gov/ct2/show/study/NCT03149926)

65 **Keywords:** Borderline, Emotion regulation, Emotional stimuli, NSSI

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73 **Article Summary**

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

83 **Strength and limitations of this study**

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

89

90 Introduction

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

101 Not surprisingly, emotional evocative material is commonly used to investigate BPD pathology.
102 Previous studies have employed various emotional stimuli such as emotional facial expression
103 (Baskin-Sommers et al., 2015; Cullen et al., 2016), pleasant or unpleasant pictures (Hazlett et al.,
104 2012; Suvak et al., 2012), pictures and video clips depicting social interactions (Koenigsberg et al.,
105 2009; Lobbestael & Arntz, 2015) or script driven imagery of an act of self-injury (Kraus et al., 2010).
106 However, research findings on emotion regulation in BPD to date are inconsistent in terms of
107 evoking emotional responses in BPD patients (Sloan et al., 2010; van Zutphen, Siep, Jacob, Goebel, &
108 Arntz, 2015). While some studies did not find evidence for abnormal emotional responsiveness in
109 BPD (Feliu-Soler et al., 2013; Kuo & Linehan, 2009; Suvak et al., 2012) others did (D. Eddie & M. E.
110 Bates, 2017; Kraus et al., 2010; C. Sauer, E. A. Arens, M. Stopsack, C. Spitzer, & S. Barnow, 2014). One
111 possible explanation for these contradictory results might be that the stimulus material was not
112 specific enough to elicit an emotional response in persons with BPD. For example, in a recent study
113 that addressed the potential difference in emotional response depending on the specificity of the
114 presented stimuli baseline emotional intensity and emotional reactivity in BPD patients were
115 compared to healthy controls. Emotional response to six discrete emotion-eliciting film clips was
116 evaluated by means of physiological and subjective reactions. Furthermore, the two groups were
117 compared regarding their emotional reaction to films containing content associated with BPD (e.g.
118 sexual abuse, emotional dependence, and abandonment/separation). Compared to healthy controls,
119 persons with BPD did not show subjectively heightened reactivity to most of the discrete emotion-
120 eliciting films but a significant stronger emotional response on "BPD-specific content" films (C.
121 Sauer et al., 2014). Those findings suggest that measuring emotion dysregulation in BPD might only
122 arise in contexts that are psychologically challenging (Sloan et al., 2010; Suvak et al., 2012). The

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3 123 actual emergence and intensity of emotions depend on an array of psychological characteristics of
4 124 the person such as personality, learning experiences and cognition, the situational context but also
5 125 on the type and intensity of the perceived stimulus (Kučera & Haviger, 2012). Emotional stimuli that
6 126 activate specific, self-relevant information seem to arouse a more intense emotional reaction than
7 127 more general emotional stimuli (Philippot, Schaefer, & Herbet, 2003). Therefore, to elicit a
8 128 distinctive and BPD specific emotional response the stimulus material has to have a high relevance
9 129 for persons with BPD and has to trigger sensitivities distinct for BPD (Suvak et al., 2012). Such a
10 130 triggering event could be the presentation of material used for non-suicidal self-injury (NSSI).

11 131 NSSI is associated with clinical and functional impairments and occurs in a variety of psychiatric
12 132 disorders (Zetterqvist, 2015). There is an ongoing scientific debate regarding the conceptualization
13 133 and diagnostic organization of NSSI. The fifth version of the Statistical and Diagnostic Manual of
14 134 Mental Disorders (DSM-5) presents Non-Suicidal Self-Injury Disorder (NSSID) as a separate
15 135 nosological entity however as a condition that requires further investigation (Association, 2013;
16 136 Zetterqvist, 2015). This shows that NSSI is not unique to BPD. However, there is a general consensus
17 137 that NSSI is related to BPD and can be considered as a core symptom of the disorder (APA, 2013;
18 138 Zetterqvist, 2015). NSSI is defined as the deliberate destruction of healthy body tissue that is not
19 139 suicidal in nature. About 90% of patients with BPD do engage in NSSI (Zanarini et al., 2008). NSSI
20 140 typically includes repeated behaviors, such as skin cutting, banging or hitting, burning, scratching,
21 141 and interfering with wound healing (Favazza, 1998). Emotion dysregulation is closely linked to NSSI
22 142 in persons with BPD. According to the experiential avoidance model, NSSI is applied to reduce or
23 143 remove aversive emotional experiences and might be maintained by negative reinforcement
24 144 (Chapman, Gratz, & Brown, 2006; Nock & Prinstein, 2004; Reitz et al., 2015).

25 145 Empirical evidence suggests that NSSI is commonly performed as emotion regulation strategy. Self-
26 146 injurers use NSSI to reduce unpleasant feelings, overcome dissociation, for self-punishment or for
27 147 the reduction of aversive inner tension (Andover & Morris, 2014; E. D. Klonsky, 2007). Typically,
28 148 NSSI is preceded by high arousal of negative emotions whereas NSSI behavior is associated with a
29 149 decrease in these emotions (E. D. Klonsky, 2007; Victor & Klonsky, 2014). For example, a decrease in
30 150 negative affect and arousal was observed in self-injurers that were asked to visualize cutting or to
31 151 engage in another painful behavior whereas the performance of a non NSSI-related task did not lead
32 152 to a decrease (E. D. Klonsky, 2007). In addition, seeing blood during NSSI seems to be an important
33 153 aspect for many self-injurers. Glenn and Klonsky (2010) investigated the role of seeing blood during
34 154 NSSI in persons with a history of NSSI. Most participants (51.6%) reported seeing blood during NSSI
35 155 was important. Furthermore, participants reported that seeing blood fulfilled multiple functions

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3 156 such as, to relieve tension (84.8%), to calm down (72.7%), to feel real (51.5%), to show the realness
4 157 of NSSI (42.4%), to help focus (33.3%) and to show that NSSI has been performed correctly/deep
5 158 enough (15.2%). A pilot study by Naoum et al. (2016) compared 20 female BPD patients and 20
6 159 healthy controls (HC) to investigate the effect of seeing blood during NSSI following stress and pain
7 160 induction. The BPD patients showed a significantly stronger decrease in arousal than the HC group,
8 161 however with no significant effects between blood and non-blood conditions. In addition, the urge
9 162 for NSSI, significantly greater decreased in the blood condition in BPD patients. While, seeing blood
10 163 did not bring greater tension relief.

11 164 Despite the connection of deficient emotion regulation and NSSI in BPD, yet no study is available
12 165 that uses stimuli depicting different stages of NSSI to investigate whether the emotional reaction of
13 166 BPD patients is gradually dependent on the stage of NSSI shown by the stimuli. A specified stimuli-
14 167 database, validated in a BPD population for evoking emotional responses in BPD is however lacking.

15 168 **This Study**

16 169 Although emotion dysregulation is recognized as a core symptom of BPD, current evidence is
17 170 inconsistent and contradictory. This could be, at least partially, explained by the use of
18 171 unsuitable and unspecific emotional stimulus material that does not tap into BPD-relevant themes.
19 172 However, to improve and extend research on emotion regulation in BPD the availability of validated
20 173 emotional stimuli that reliably elicit emotional reactions distinct for BPD is a necessary prerequisite.

21 174 This study aims to develop and validate an emotional picture set, EPSI (emotional picture set with
22 175 scenes of self-injury), relevant for BPD. In a second step, the emotional reaction will be assessed by
23 176 means of a self-report measurement as well as by a psychophysiological assessment of the
24 177 emotional reaction in a sample of persons with BPD who engage in NSSI, in a depressive control
25 178 group and in a sample of matched healthy controls. Furthermore, participants are asked to indicate
26 179 how strong the pictures relate to their person or biography. EPSI depicts objects frequently used for
27 180 NSSI and show the application of those objects at different stages of NSSI (pre-NSSI, NSSI, post-
28 181 NSSI). As NSSI can be associated with different emotional reactions depending on the stage of NSSI,
29 182 differences in the emotional reaction are expected for persons with BPD for the specific NSSI
30 183 categories. In a pre-NSSI stage (preparing for NSSI), negative affect, arousal and tension are
31 184 expected to be strongest. When starting NSSI, negative affect, arousal and tension might start to
32 185 decrease. On a post-NSSI stage (successfully performed NSSI, seeing blood), an even stronger
33 186 decrease of emotions and a sense of relief and relaxation is expected. It is hypothesized that the
34 187 control groups show the opposite emotional reaction with lowest emotional response when seeing

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

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

195 **Objectives**

196 Primary outcome variables are self-rated emotional reaction measured with the Self-Assessment-
197 Manikin (SAM, (M. M. Bradley & P. J. Lang, 1994)); psychophysiological measurements of emotion
198 will be assessed by heart rate variability (HRV) as indicator of Autonomic Nervous System (ANS)
199 activity and the analyses of facial expression as measured with Noldus FaceReader software
200 (Noldus Information Technology, www.noldus.com). As a secondary outcome variable, Self-
201 reference of EPSI will be measured on a 5-point Likert-scale with the item 'How much do you see a
202 relation to your own person/ to your biography?' from 1 (not at all) to 5 (very much) (C. Sauer et al.,
203 2014).

204 Primary objectives:

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

211 Secondary objectives:

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

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3 219 5. To investigate if self-rated emotional response does correlate with psychophysiological
4 220 measurements of emotional response within and between groups.
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8 221 **Methods and analysis**

9 222 **Participants**

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11 223 In total 90 participants (30 BPD patients, 30 depressed patients, and 30 healthy control subjects)
12 224 aged from 18-60 years will be recruited. To control for altered autonomic response all participants
13 225 have to be free of severe, persistent neurological disorders (in particular, epilepsy, multiple
14 226 sclerosis, stroke or neurodegenerative disease) and are not allowed to be currently medicated with
15 227 antihistamines, neuroleptic medication, tranquilizers or beta blockers. Further, the BPD patients
16 228 need to have a lifetime history of self-injury. Further exclusion criteria for the BPD patients are:
17 229 psychotic disorders, current major depressive episode, acute suicidal crisis. The patients in the
18 230 depressed control group need to have a depressive episode > 2weeks. The control groups will be
19 231 matched to the BPS group for age and sex. The healthy control group has not to exhibit a current
20 232 psychiatric disorder or history of self-injury.
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30 233 ***Patient and public involvement***

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32 234 Patients were not involved in the development of the research question, outcome measures or study
33 235 design.
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37 236 **Diagnostic procedure**

38 237 Assessments of DSM-IV Personality Disorders (ADP-IV) (Doering et al., 2007; Schotte & De Doncker,
39 238 1994) and the Borderline Symptom Checklist (BSL-23) (Wolf et al., 2009) will be used to verify the
40 239 diagnosis of BPD and to assess BPD symptoms. The structured clinical interview (SKID I,II) will be
41 240 performed to assess psychiatric disorders (Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997).
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46 241 To record the history and methods of self-injury, the Inventory of Statements about Self-Injury and
47 242 the Self-Harm Behavior Questionnaire will be applied (Gutierrez, Osman, Barrios, & Kopper, 2001;
48 243 Klonsky & Glenn, 2009). The general psychopathology will be recorded with the symptom
49 244 checklist-90 (SCL-90) (Franke, 2002). Depressive symptoms will be self-rated with the Beck
50 245 Depression Inventory (BDI) (Beck, Steer, & Brown, 1996). Since the study will assess the emotional
51 246 processing of images, the current mood and stress of the participants could have an influence.
52 247 Therefore, they will be asked how emotionally strained and charged they are at the moment before
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3 248 and during testing on a Likert-scale ranging from 0-10. To check on the patient, a short break in the
4 249 middle of the experiment is planned. Acute somatic and psychological dissociation will be assessed
5
6 250 by the short version of the Dissociative State Scale (DSS) (Stiglmayr, Braakmann, Haaf, Stieglitz, &
7
8 251 Bohus, 2003). Further, a demographic questionnaire, as well as the Edinburgh Handedness
9
10 252 Inventory (Oldfield, 1971) will be applied.

11 12 253 **Stimuli**

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14 254 Photographs and image processing will be made by a professional photographer. Three categories
15
16 255 of objects and scenes for NSSI are planned to be photographed: objects that are frequently used for
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18 256 NSSI by BPD patients (self-injury objects; SIO), scenic presentation of usage shortly before the injury
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20 257 (SIO_{bi}), and scenic presentation during the usage of SIO (SIO_{dur}). SIO's will be selected based on the
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22 258 prevalence of usage decided from psychiatrists' expertise and on the existing literature (Brown et
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24 259 al., 2018; E David Klonsky, 2007; Jennifer Svaldi, Christina Dorn, Swantje Matthies, & Alexandra
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26 260 Philipsen, 2012). Actors that are instructed by the experimenters will play the mimicking of the
27
28 261 usage of SIO's. Here, only the arms will be visible. Each image that involves body-parts will be acted
29
30 262 by a man and a woman to prevent gender bias in the judgement (see Figure 2 for examples from
31
32 263 EPSI for the three categories of objects and scenes).

33 264 **Experimental Design**

34 265 Participants will be asked to watch the images and to rate their current emotion on a scale of
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36 266 arousal, dominance, and valence. For this purpose, the self-assessment manikin (SAM) will be used
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38 267 (Margaret M Bradley & Peter J Lang, 1994). As control images to the SIO images, neutral objects
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40 268 (e.g., tools) will be shown (see Figure 1 for examples of neutral images). The neutral images will be
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42 269 taken from an existing and validated image database (Blechert, Meule, Busch, & Ohla, 2014). After
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44 270 half of the stimuli, a break will be done to check for the emotional status of the participants to assess
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46 271 and to prevent dissociations (Jaeger et al., 2017). Image presentation will be pseudorandomized
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48 272 across all categories. In order to prevent decomposition of the patients to the content of the stimuli,
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50 273 the patients will be monitored during the whole session by a therapist to intervene when necessary.
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52 274 In total 90 images will be shown (45 EPSI/ 45 neutral) each shown for 500ms followed by the
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54 275 judgement of the SAM. judgement of the SAM (see Figure 3 for the study design).

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56 276 *-Please insert Figure1-*

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58 277 **Figure 1.** *Examples of neutral pictures from food-pics: an image database for experimental research on eating and appetite*

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3 279 *-Please insert Figure2-*

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7 281 **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
8 282 NSSI by BPD patients (self-injury objects; SIO), scenic presentation of usage shortly before the injury (SIO_{bi}), and scenic presentation during
9 283 the usage of SIO (SIO_{dur}).

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15 285 **Physiological Measurement**

16 286 **Autonomic nervous system**

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19 287 Assessment of the heart rate variability (HRV) is a valid and reliable indicator of the Autonomic
20 288 Nervous System (ANS) and is considered as a transdiagnostic marker of psychopathology (Koenig et
21 289 al., 2017; Wilson et al., 2016). Heart rate will be continuously recorded with an EC-12R rest-ecg.
22
23 290 Three electrodes will be attached according to Einthoven's triangle plus a ground at the right lower
24 291 limb (Einthoven, Fahr, & De Waart, 1913). HRV will be derived through a frequency domain analysis
25
26 292 by taking the time-domain representation of the inter-beat-interval (IBI) and to convert it with a
27 293 Fourier transformation to the frequency domain (Allen, Chambers, & Towers, 2007). Since we aim a
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29 294 recording of time at the length of the experiment, the ECG measurement can be considered as a
30
31 295 short-term recording. Hence, the low-frequency band (LF; 0.04-0.15 Hz) and the high-frequency
32 296 band (HF; 0.15-0.4 Hz) will be the frequencies of interest (Thayer, Hansen, & Johnsen, 2010).

33 34 35 297 **Emotional face activation**

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37
38 298 The universal emotions happy, sad, angry, surprised, scared, disgusted and neutral as they were
39 299 proposed by Ekman (Ekman & Keltner, 1970) will be measured with Noldus FaceReader software
40 300 (Noldus Information Technology, www.noldus.com). The program detects facial expressions
41 301 reliably and was successfully applied in numerous studies (Boerner, Chambers, McGrath, LoLordo,
42 302 & Uher, 2017; Dalton, Jimenez, & Noussair, 2017). Throughout the whole session, the participants
43 303 will be videotaped with a webcam. A frame-by-frame analysis will be done by the software. Over
44 304 500 key points of the participant's face are localized and compared to a database of annotated
45 305 images. The intensity of the universal emotions is decoded on a scale from 0 to 1, where 0 means
46 306 that the emotion is not present and 1 indicates an intensive emotional reaction. In addition to the
47 307 universal emotions, the software also captures valence and arousal. Valence is calculated as the
48 308 intensity of 'happy' minus the intensity of the negative expressions (angry, scared and disgusted)
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50 309 with the highest intensity. For arousal, the mean activation over the last 60 seconds of certain

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3 310 muscle groups in the face is subtracted from the current muscle activation. The mean of the five
4 311 highest values results in a value of arousal.

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7 312 To prevent that the software has a bias towards certain expressions a calibration will be done with a
8 313 neutral look of each participant.

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13 315 *-Please insert Figure3-*

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20 **Figure 3. Study design.**

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22 23 319 **Statistical analysis**

24 25 320 **Stimulus Validation**

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27 321 Interrater reliability will be assessed with Krippendorff's alpha. The advantage over other statistical
28 322 methods to assess interrater reliability is that Krippendorff's alpha allows more than two raters
29 323 (unlike Cohen's Kappa) and also can handle missing data points (unlike Fleiss Kappa) (Zapf, Castell,
30 324 Morawietz, & Karch, 2016). The assumption of Krippendorff's alpha is based on the observed
31 325 disagreement corrected for disagreement by chance, which is calculable to a range of -1 to 1, where
32 326 1 illustrates perfect agreement, 0 means no agreement beyond chance and negative values indicate
33 327 inverse agreement (Krippendorff, 1970; Zapf et al., 2016). Bootstrapped confidence intervals will be
34 328 used since the distribution is not known, the derivation of the correct standard error is not straight
35 329 forward, and the type 1 error level is acceptable (McKenzie et al., 1996; Vanbelle & Albert, 2008;
36 330 Zapf et al., 2016). Krippendorff's alpha will be computed for each SAM-dimension for each stimuli
37 331 category.

38 39 332 **Behavioral Data**

40 333 If the data show normal distribution, a 2x3x4 between subjects analysis of variance (ANOVA) will be
41 334 computed with the factors group, SAM-evaluation and stimuli category. Further, the questionnaire-
42 335 scores will be correlated with the SAM-evaluations for each stimulus category. To assess gender
43 336 bias, a linear regression will be performed to rule out possible performance differences.

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45 337

338 **Physiological Data**

339 ***HRV***

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

342

343 ***Emotional Face Activation***

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

349 **Sample size justification**

350 Using G*Power to estimate the effect size, based on a fixed effects ANOVA with 30 participants per
351 group yield in a large effect size (0.62) with a power of 0.66 (Faul, Erdfelder, Lang, & Buchner,
352 2007). The size of the groups were derived from earlier studies that compares the affective reaction
353 of BPS patients with healthy control while image watching (David Eddie & Marsha E Bates, 2017;
354 Christina Sauer, Elisabeth A Arens, Malte Stopsack, Carsten Spitzer, & Sven Barnow, 2014).

355 **Ethics and dissemination**

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

364

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

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3 582 **Authors' contributions**
4

5 583 KB, MS: study design, literature search, figures, writing
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7 584 PS: study design, literature search, writing, supervision
8

9
10 585 CS: study design, supervision
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12 586 AP: study design, literature search, writing, supervision
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17

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19
20 589 for-profit sectors.
21
22

23 590 **Competing interests statement**
24

25 591 KB, MS, PS, CS declare that the research was conducted in the absence of any commercial or
26
27 592 financial relationships that could be construed as a potential conflict of interest.
28

29 593 AP declares that she served on advisory boards, gave lectures, performed phase 3 studies, or
30
31 594 received travel grants within the last 3 years from Eli Lilly and Co, Lundbeck, MEDICE Arzneimittel,
32
33 595 Pütter GmbH and Co KG, Novartis, Servier, and Shire; and has authored books and articles on ADHD
34
35 596 published by Elsevier, Hogrefe, Schattauer, Kohlhammer, Karger, and Springer.
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42 599 We used the SPIRIT checklist when writing our report (Chan et al., 2013)
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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).

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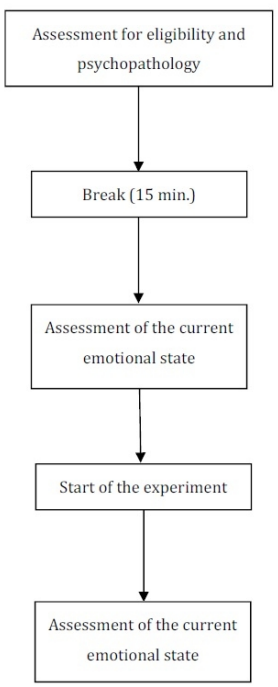


Figure 3. Study design.

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.

Upload your completed checklist as an extra file when you submit to a journal.

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

1	Roles and	#5b	Name and contact information for the trial sponsor	n/a
2	responsibilities:			
3	sponsor contact			
4	information			
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7	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	n/a
8	responsibilities:		collection, management, analysis, and interpretation of	
9	sponsor and funder		data; writing of the report; and the decision to submit the	
10			report for publication, including whether they will have	
11			ultimate authority over any of these activities	
12				
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15	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	n/a
16	responsibilities:		centre, steering committee, endpoint adjudication	
17	committees		committee, data management team, and other individuals or	
18			groups overseeing the trial, if applicable (see Item 21a for	
19			data monitoring committee)	
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24	Background and	#6a	Description of research question and justification for	5-8
25	rationale		undertaking the trial, including summary of relevant studies	
26			(published and unpublished) examining benefits and harms	
27			for each intervention	
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31	Background and	#6b	Explanation for choice of comparators	7-8
32	rationale: choice of			
33	comparators			
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36	Objectives	#7	Specific objectives or hypotheses	8-9
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39	Trial design	#8	Description of trial design including type of trial (eg, parallel	9-10
40			group, crossover, factorial, single group), allocation ratio,	
41			and framework (eg, superiority, equivalence, non-inferiority,	
42			exploratory)	
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46	Study setting	#9	Description of study settings (eg, community clinic,	9
47			academic hospital) and list of countries where data will be	
48			collected. Reference to where list of study sites can be	
49			obtained	
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52	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	
53			eligibility criteria for study centres and individuals who will	
54			perform the interventions (eg, surgeons, psychotherapists)	9
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58	Interventions:	#11a	Interventions for each group with sufficient detail to allow	9-13
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1	description		replication, including how and when they will be administered	
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4	Interventions:	#11b	Criteria for discontinuing or modifying allocated	9, 10
5	modifications		interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	
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10	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9, 10
11	adherence			
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16	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
17	concomitant care			
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20	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
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31	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
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38	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
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45	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9,14
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49	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
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1	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	n/a
2	concealment		central telephone; sequentially numbered, opaque, sealed	
3	mechanism		envelopes), describing any steps to conceal the sequence	
4			until interventions are assigned	
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7	Allocation:	#16c	Who will generate the allocation sequence, who will enrol	n/a
8	implementation		participants, and who will assign participants to	
9			interventions	
10				
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13	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,	n/a
14			trial participants, care providers, outcome assessors, data	
15			analysts), and how	
16				
17				
18	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	n/a
19	emergency		permissible, and procedure for revealing a participant's	
20	unblinding		allocated intervention during the trial	
21				
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24	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline,	9 – 11
25			and other trial data, including any related processes to	
26			promote data quality (eg, duplicate measurements, training	
27			of assessors) and a description of study instruments (eg,	
28			questionnaires, laboratory tests) along with their reliability	
29			and validity, if known. Reference to where data collection	
30			forms can be found, if not in the protocol	
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35	Data collection plan:	#18b	Plans to promote participant retention and complete follow-	9-11
36	retention		up, including list of any outcome data to be collected for	
37			participants who discontinue or deviate from intervention	
38			protocols	
39				
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41				
42	Data management	#19	Plans for data entry, coding, security, and storage, including	11-14
43			any related processes to promote data quality (eg, double	
44			data entry; range checks for data values). Reference to	
45			where details of data management procedures can be	
46			found, if not in the protocol	
47				
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49				
50	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary	13-14
51			outcomes. Reference to where other details of the statistical	
52			analysis plan can be found, if not in the protocol	
53				
54				
55	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	14
56	analyses		adjusted analyses)	
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1	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	14
2	population and		adherence (eg, as randomised analysis), and any statistical	
3	missing data		methods to handle missing data (eg, multiple imputation)	
4				
5				
6	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary	n/a
7	formal committee		of its role and reporting structure; statement of whether it is	
8			independent from the sponsor and competing interests; and	
9			reference to where further details about its charter can be	
10			found, if not in the protocol. Alternatively, an explanation of	
11			why a DMC is not needed	
12				
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16	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	n/a
17	interim analysis		including who will have access to these interim results and	
18			make the final decision to terminate the trial	
19				
20				
21	Harms	#22	Plans for collecting, assessing, reporting, and managing	10
22			solicited and spontaneously reported adverse events and	
23			other unintended effects of trial interventions or trial conduct	
24				
25				
26				
27	Auditing	#23	Frequency and procedures for auditing trial conduct, if any,	n/a
28			and whether the process will be independent from	
29			investigators and the sponsor	
30				
31				
32	Research ethics	#24	Plans for seeking research ethics committee / institutional	3
33	approval		review board (REC / IRB) approval	
34				
35				
36	Protocol	#25	Plans for communicating important protocol modifications	n/a
37	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
38			relevant parties (eg, investigators, REC / IRBs, trial	
39			participants, trial registries, journals, regulators)	
40				
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43	Consent or assent	#26a	Who will obtain informed consent or assent from potential	15
44			trial participants or authorised surrogates, and how (see	
45			Item 32)	
46				
47				
48	Consent or assent:	#26b	Additional consent provisions for collection and use of	n/a
49	ancillary studies		participant data and biological specimens in ancillary	
50			studies, if applicable	
51				
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53	Confidentiality	#27	How personal information about potential and enrolled	9
54			participants will be collected, shared, and maintained in	
55			order to protect confidentiality before, during, and after the	
56			trial	
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1	Declaration of	#28	Financial and other competing interests for principal	22
2	interests		investigators for the overall trial and each study site	
3				
4	Data access	#29	Statement of who will have access to the final trial dataset,	n/a
5			and disclosure of contractual agreements that limit such	
6			access for investigators	
7				
8				
9				
10	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	n/a
11	trial care		compensation to those who suffer harm from trial	
12			participation	
13				
14				
15	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	15
16	trial results		results to participants, healthcare professionals, the public,	
17			and other relevant groups (eg, via publication, reporting in	
18			results databases, or other data sharing arrangements),	
19			including any publication restrictions	
20				
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22				
23				
24	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	n/a
25	authorship		professional writers	
26				
27	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	n/a
28	reproducible		participant-level dataset, and statistical code	
29	research			
30				
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32				
33	Informed consent	#32	Model consent form and other related documentation given	15
34	materials		to participants and authorised surrogates	
35				
36				
37	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	n/a
38			biological specimens for genetic or molecular analysis in the	
39			current trial and for future use in ancillary studies, if	
40			applicable	
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 44 BY-ND 3.0. This checklist can be completed online using <https://www.goodreports.org/>, a tool made
 45 by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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Protocol article: Development and validation of an emotional picture set of self-injury (EPSI) for borderline personality disorder

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Manuscripts

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

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48 **Abstract**

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

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

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

63 **Trial registration number:** clinicaltrials.gov: NCT03149926

64 **Keywords:** Borderline, Emotion regulation, Emotional stimuli, NSSI

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3 74 **Strengths and limitations of this study**
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- 5 75 • Controlled study design to develop emotional stimuli relevant for BPD
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7 76 • Emotional reaction is assessed by subjective as well as objective measurements
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9 77 • Emotion evocation is limited to NSSI however other emotional trigger (e.g. social
10 78 interaction) are not investigated
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12 79 • Limited to BPD patients that actually engage in NSSI
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For peer review only

81 Introduction

82 Borderline personality disorder (BPD) is a severe psychiatric disorder that is characterized by
83 impairments in interpersonal, cognitive, and emotional functioning^{1 2}. Pervasive problems in affect
84 regulation have been identified as the central area of dysfunction in BPD. BPD even has been
85 conceptualized as a disorder of the emotion regulation system³. Emotion dysregulation comprises
86 high emotional vulnerability in conjunction with an inability to regulate emotions. Emotional
87 vulnerability in individuals with BPD is characterized by high sensitivity to emotional stimuli,
88 unusual emotional intensity and a slow return to emotional baseline (emotions are long-lasting). In
89 addition, the identification, expression, and inhibition of emotions are impaired³⁻⁵.

90 Not surprisingly, emotionally evocative material is commonly used to investigate BPD pathology.
91 Previous studies have employed various emotional stimuli such as emotional facial expression^{6 7},
92 pleasant or unpleasant pictures^{8 9}, pictures and video clips depicting social interactions^{10 11} or
93 script-driven imagery of an act of self-injury¹². However, research findings on emotion regulation in
94 BPD to date are inconsistent in terms of evoking emotional responses in BPD patients^{13 14}. While
95 some studies did not find evidence for abnormal emotional responsiveness in BPD^{9 15 16} others did
96^{12 17 18}. One possible explanation for these contradictory results might be that the stimulus material
97 was not specific enough to elicit an emotional response in persons with BPD. For example, in a
98 recent study that investigated difference in emotional response and specificity of the presented
99 stimuli, baseline emotional intensity and emotional reactivity in BPD patients were compared to
100 healthy controls. Emotional response to six discrete emotion-eliciting film clips was evaluated by
101 means of physiological and subjective reactions. Furthermore, the two groups were compared
102 regarding their emotional reaction to films containing content associated with BPD (e.g. sexual
103 abuse, emotional dependence, and abandonment/separation). Compared to healthy controls,
104 persons with BPD did not show subjectively heightened reactivity to most of the discrete emotion-
105 eliciting films but a significantly stronger emotional response to “BPD-specific content” films¹⁸.
106 These findings suggest that measuring emotional responses that are characteristic for BPD only
107 make sense in contexts that are psychologically challenging^{9 13}. The actual emergence and intensity
108 of emotions depend on an array of psychological characteristics of the person such as personality,
109 learning experiences and cognition, the situational context but also on the type and intensity of the
110 perceived stimulus¹⁹. Emotional stimuli that activate specific, self-relevant information seem to
111 arouse a more intense emotional reaction than more general emotional stimuli^{5 20}. Therefore, to
112 elicit a distinctive and BPD-specific emotional response the stimulus material has to have a high

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3 113 relevance for persons with BPD and has to trigger sensitivities distinct for BPD ^{5 9}. Such a triggering
4 114 event could be the presentation of material used for non-suicidal self-injury (NSSI).

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7 115 NSSI is associated with clinical and functional impairments and occurs in a variety of psychiatric
8 116 disorders ²¹. There is an ongoing scientific debate regarding the conceptualization and diagnostic
9 117 organization of NSSI. The fifth version of the Diagnostic and Statistical Manual of Mental Disorders
10 118 (DSM-5) presents Non-Suicidal Self-Injury Disorder (NSSID) as a separate nosological entity
11 119 however as a condition that requires further investigation ^{21 22}. This shows that NSSI is not unique to
12 120 BPD. However, there is a general consensus that NSSI is related to BPD and can be considered as a
13 121 core symptom of the disorder ^{1 21}. NSSI is defined as the deliberate destruction of healthy body
14 122 tissue that is not suicidal in nature. About 90% of patients with BPD do engage in NSSI ²³. NSSI
15 123 typically includes repeated behaviors, such as skin cutting, banging or hitting, burning, scratching,
16 124 and interfering with wound healing ²⁴. Emotion dysregulation is closely linked to NSSI in persons
17 125 with BPD. According to the experiential avoidance model, NSSI is applied to reduce or remove
18 126 aversive emotional experiences and might be maintained by negative reinforcement ²⁵⁻²⁷.

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27 127 Empirical evidence suggests that NSSI is commonly performed as emotion regulation strategy. Self-
28 128 injurers use NSSI to reduce unpleasant feelings, overcome dissociation, for self-punishment or for
29 129 the reduction of aversive inner tension ^{28 29}. Typically, NSSI is preceded by high arousal of negative
30 130 emotions whereas NSSI behavior is associated with a decrease in these emotions ^{29 30}. For example,
31 131 a decrease in negative affect and arousal was observed in self-injurers who were asked to visualize
32 132 cutting or to engage in another painful behavior whereas the performance of a non-NSSI-related
33 133 task did not lead to a decrease ²⁹. In addition, seeing blood during NSSI seems to be an important
34 134 aspect for many self-injurers. Glenn and Klonsky ³¹ investigated the role of seeing blood during NSSI
35 135 in persons with a history of NSSI. Most participants (51.6%) reported seeing blood during NSSI was
36 136 important. Furthermore, participants reported that seeing blood fulfilled multiple functions, such as
37 137 to relieve tension (84.8%), to calm down (72.7%), to feel real (51.5%), to show the realness of NSSI
38 138 (42.4%), to help focus (33.3%), and to show that NSSI has been performed correctly/deep enough
39 139 (15.2%). A pilot study by Naoum, et al. ³² compared 20 female BPD patients and 20 healthy controls
40 140 (HC) to investigate the effect of seeing blood during NSSI following stress and pain induction. The
41 141 BPD patients showed a significantly stronger decrease in arousal than the HC group, however with
42 142 no significant effects between blood and non-blood conditions. In addition, the urge for NSSI,
43 143 significantly greater decreased in the blood condition in BPD patients. Seeing blood did not result in
44 144 greater relief of tension, though.

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3 145 Despite the connection of deficient emotion regulation and NSSI in BPD, yet no study is available
4 146 that uses stimuli depicting different stages of NSSI to investigate whether the emotional reaction of
5 147 BPD patients is gradually dependent on the stage of NSSI shown by the stimuli. A specified stimuli-
6 148 database, validated in a BPD population for evoking emotional responses in BPD is lacking.
9

10 149 **This Study**

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12 150 Although emotion dysregulation is recognized as a core symptom of BPD, current evidence is
13 151 inconsistent and contradictory. This could be, at least partially, explained by the use of unsuitable
14 152 and unspecific emotional stimulus material that does not tap into BPD-relevant themes. However, to
15 153 improve and extend research on emotion regulation in BPD the availability of validated emotional
16 154 stimuli that reliably elicit emotional reactions distinct for BPD is a necessary prerequisite.

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21 155 This study aims to develop and validate an emotional picture set, EPSI (emotional picture set with
22 156 scenes of self-injury), relevant for BPD. In a second step, the emotional reaction will be assessed by
23 157 means of a self-report measurement as well as by a psychophysiological assessment of the
24 158 emotional reaction in a sample of persons with BPD who engage in NSSI, in a depressive control
25 159 group, and in a sample of matched healthy controls. Furthermore, participants are asked to indicate
26 160 how strong the pictures relate to their person or biography. EPSI depicts objects frequently used for
27 161 NSSI and shows the application of these objects at different stages of NSSI (objects only, pre-NSSI,
28 162 NSSI, during-NSSI). As NSSI can be associated with different emotional reactions depending on the
29 163 stage of NSSI, differences in the emotional reaction are expected for persons with BPD for the
30 164 specific NSSI categories. In the pre-NSSI stage (preparing for NSSI), negative affect, arousal, and
31 165 tension are expected to be strongest. When starting NSSI, negative affect, arousal, and tension
32 166 might start to decrease. In the during-NSSI stage (successfully performed NSSI, seeing blood), an
33 167 even stronger decrease of emotions and a sense of relief and relaxation is expected. It is
34 168 hypothesized that the control groups show the opposite emotional reaction with lowest emotional
35 169 response when seeing pictures of a pre-NSSI stage and strongest emotional response when
36 170 watching during-NSSI pictures. Furthermore, BPD participants are expected to report higher self-
37 171 reference regarding the pictures in comparison to the healthy controls.
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49 172 To investigate if our database is BPD relevant, the evaluations of the NSSI images will be compared
50 173 to neutral images and also to two different control groups. This study allows investigating to what
51 174 extent EPSI can elicit an emotional response distinctive for persons with BPD and if the emotional
52 175 response differs with regard to the stage of NSSI.
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176 Objectives

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

184 Primary objectives:

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

189 Secondary objectives:

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

200 Methods and analysis

201 Participants

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

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3 206 antihistamines, neuroleptic medication, tranquilizers or beta blockers. Further, the BPD patients
4 207 need to have a lifetime history of self-injury. Exclusion criteria for the BPD patients are psychotic
5 208 disorders, current major depressive episode, and acute suicidal crisis. The patients in the depressed
6 209 control group need to suffer from current major depressive episode (depressive symptoms for at
7 210 least 2 weeks). Depressive patients who also met diagnostic criteria for a psychotic disorder will be
8 211 excluded. The healthy control group must not exhibit a current psychiatric disorder or history of
9 212 self-injury. Additional exclusion criteria for both control groups are attempted suicide or current
10 213 suicide ideation. The control groups will be matched to the BPD group for age and sex.

16 17 214 ***Patient and public involvement***

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19 215 Patients were not involved in the development of the research question, outcome measures or study
20 216 design.

22 23 217 **Diagnostic procedure**

24
25 218 Assessments of DSM-IV Personality Disorders (ADP-IV)^{34 35} and the Borderline Symptom Checklist
26 219 (BSL-23)³⁶ will be used to verify the diagnosis of BPD and to assess BPD symptoms. The structured
27 220 clinical interview (SCID I,II) will be performed to assess psychiatric disorders³⁷.

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31 221 To record the history and methods of self-injury, the Inventory of Statements about Self-Injury
32 222 (ISAS) and the Self-Harm Behavior Questionnaire (SHQ) will be applied^{38 39}. Any outcome above
33 223 zero, that means NSSI has been performed, on the ISAS or SHQ will be an exclusion criterion. The
34 224 general psychopathology will be recorded with the symptom checklist-90 (SCL-90)⁴⁰. Depressive
35 225 symptoms will be self-rated with the Beck Depression Inventory (BDI)⁴¹. Since the study will assess
36 226 the emotional processing of images, the current mood and stress of the participants could have an
37 227 influence. Therefore, they will be asked how emotionally strained and charged they are at the
38 228 moment before and during testing on a Likert-scale ranging from 0-10. To check on the patient, a
39 229 short break in the middle of the experiment is planned. Acute somatic and psychological
40 230 dissociation will be assessed by the short version of the Dissociative State Scale (DSS)⁴². Further, a
41 231 demographic questionnaire, as well as the Edinburgh Handedness Inventory⁴³ will be applied.

42 43 44 45 46 47 48 49 232 **Stimuli**

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51 233 Photographs and image processing will be made by a professional photographer. Three categories
52 234 of objects and scenes for NSSI are planned to be photographed: objects that are frequently used for
53 235 NSSI by BPD patients (self-injury objects; SIO), scenic presentation of usage shortly before the injury
54 236 (SIO_{bi}), and scenic presentation during the usage of SIO (SIO_{dur}). SIOs will be selected based on the

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3 237 prevalence of usage decided from psychiatrists' expertise and on the existing literature ⁴⁴⁻⁴⁶. Actors
4 238 that are instructed by the experimenters will play the mimicking of the usage of SIOs. Here, only the
5 239 arms will be visible. Each image that involves body-parts will be acted by a man and a woman to
6 240 prevent gender bias in the judgment (see Figure 1 for examples from EPSI for the three categories of
7 241 objects and scenes).

242 **Experimental Design**

14 243 Participants will be asked to watch the images and to rate their current emotion on a scale of
15 244 arousal, dominance, and valence. For this purpose, the Self-Assessment Manikin (SAM) will be used
16 245 ⁴⁷. As control images to the SIO images, neutral objects (e.g., tools) will be shown (see Figure 2 for
17 246 examples of neutral images). The neutral images will be taken from an existing and validated image
18 247 database ⁴⁸. After half of the stimuli, a break will be done to check for the emotional status of the
19 248 participants to assess and to prevent dissociations ⁴⁹. Image presentation and SAM rating-screens
20 249 will be pseudorandomized across all categories. In order to prevent decomposition of the patients to
21 250 the content of the stimuli, the patients will be monitored during the whole session by a therapist to
22 251 intervene when necessary. In total 90 images will be shown (45 EPSI/ 45 neutral) each shown for
23 252 500 ms followed by the judgment of the SAM (see Figure 3 for the study design). At the end of the
24 253 experiment, participants will perform a self-reference rating on all EPSI picture. This will be
25 254 measured by means of a 5-point scale with anchors: 1="Not at all related to me" s and 5= "Definitely
26 255 related to me". See table 1 for study timeline flow.

256
257 *-Please insert Figure 1-*

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260 **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*
261 *NSSI by BPD patients (self-injury objects; SIO), scenic presentation of usage shortly before the injury (SIO_b), and scenic presentation during*
262 *the usage of SIO (SIO_{dur}).*

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264 *-Please insert Figure 2-*

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

266 **Physiological Measurement**

267 **Autonomic nervous system**

268 Assessment of the heart rate variability (HRV) is a valid and reliable indicator of the autonomic
269 nervous system (ANS) and is considered as a transdiagnostic marker of psychopathology^{50 51}. Heart
270 rate will be continuously recorded with an EC-12R PC-based resting ECG system (Labtech,
271 Debrecen, Hungary). Three electrodes will be attached according to Einthoven's triangle plus a
272 ground at the right lower limb⁵². HRV will be derived through a frequency domain analysis by
273 taking the time-domain representation of the inter-beat-interval (IBI) and to convert it with a
274 Fourier transformation to the frequency domain⁵³. Since we aim a recording of time at the length of
275 the experiment, the ECG measurement can be considered as a short-term recording. Hence, the low-
276 frequency band (LF; 0.04-0.15 Hz) and the high-frequency band (HF; 0.15-0.4 Hz) will be the
277 frequencies of interest⁵⁴. Processing of the HRV-data will be done with the Kubios HRV software
278 (www.kubios.com)⁵⁵. A threshold-based artifact correction algorithm, as it is implemented in the
279 Kubios software will be performed. To separate ectopic and misplaced beats from the normal sinus
280 rhythm, the automatic artifact correction algorithm will be used⁵⁵. Further, heart rate reactivity will
281 be calculated.

282 **Emotional face activation**

283 The universal emotions happy, sad, angry, surprised, scared, disgusted, and neutral as proposed by
284 Ekman⁵⁶ will be measured with Noldus FaceReader software (Noldus Information Technology,
285 www.noldus.com). The program detects facial expressions reliably and was successfully applied in
286 numerous studies^{57 58}. Throughout the whole session, the participants will be videotaped with a
287 webcam. A frame-by-frame analysis will be done by the software. Over 500 key points of the
288 participant's face are localized and compared to a database of annotated images. The intensity of the
289 universal emotions is decoded on a scale from 0 to 1, where 0 means that the emotion is not present
290 and 1 indicates an intensive emotional reaction. In addition to the universal emotions, the software
291 also captures valence and arousal. Valence is calculated as the intensity of 'happy' minus the
292 intensity of the negative expressions (angry, scared, and disgusted) with the highest intensity. For
293 arousal, the mean activation over the last 60 seconds of certain muscle groups in the face is
294 subtracted from the current muscle activation. The mean of the five highest values results in a value
295 of arousal.

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

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12 **Figure 3.** A) *Study design.* B) *Experimental paradigm;* NSSI=non-suicidal self-injury; SAM I/II/III=Self-Assessment Manikin
13 302 (Dominance, Arousal, and Valence) presented pseudorandomized

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15 303 **Statistical analysis**

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18 304 **Stimulus Validation**

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20 305 Interrater reliability will be assessed with Krippendorff's alpha. The advantage over other statistical
21 306 methods to assess interrater reliability is that Krippendorff's alpha allows more than two raters
22 307 (unlike Cohen's Kappa) and also can handle missing data points (unlike Fleiss Kappa)⁵⁹. The
23 308 assumption of Krippendorff's alpha is based on the observed disagreement corrected for
24 309 disagreement by chance, which is calculable to a range of -1 to 1, where 1 illustrates perfect
25 310 agreement, 0 means no agreement beyond chance, and negative values indicate inverse agreement
26 311^{59 60}. Bootstrapped confidence intervals will be used since the distribution is not known, the
27 312 derivation of the correct standard error is not straightforward, and the type 1 error level is
28 313 acceptable^{59 61 62}. Krippendorff's alpha will be computed for each SAM-dimension for each stimuli
29 314 category.

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35 315 **Behavioral Data**

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38 316 If the data show normal distribution, a 2x3x4 between-subjects analysis of variance (ANOVA) will
39 317 be computed with the factors group, SAM-evaluation, and stimulus category. Further, the
40 318 questionnaire scores will be correlated with the SAM-evaluations for each stimulus category. To
41 319 assess gender bias, a linear regression will be performed to rule out possible performance
42 320 differences.

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51 322 **Physiological Data**

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54 323 **HRV**

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

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327 ***Emotional Face Activation***

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

333 **Sample size justification**

334 Based on calculations with G*Power, a fixed effects ANOVA with 30 participants per group will yield
 335 a large effect size (0.62) with a power of 0.66.⁶³. The size of the groups was derived from earlier
 336 studies comparing the affective reaction of BPD patients with healthy controls while watching
 337 images ⁶⁴⁶⁵.

338 **Table 1** Study timeline flow

Months	1 st year			2 st year				3 rd 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

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343 **Ethics and dissemination**

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

352

353 We used the SPIRIT checklist when writing our report ⁶⁶

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3 **580 Authors' contributions**
4

5 581 KB, MS: study design, literature search, figures, writing
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7 582 PS: study design, literature search, writing, supervision
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10 583 CS: study design, supervision
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12 584 AP: study design, literature search, writing, supervision
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16 **585 Funding statement**
17

18 586 This research received no specific grant from any funding agency in the public, commercial or not-
19 for-profit sectors.
20 587
21
22

23 **588 Competing interests statement**
24

25 589 KB, MS, PS, CS declare that the research was conducted in the absence of any commercial or
26 financial relationships that could be construed as a potential conflict of interest.
27 590
28

29 591 AP declares that she served on advisory boards, gave lectures, performed phase 3 studies, or
30 received travel grants within the last 3 years from Eli Lilly and Co, Lundbeck, MEDICE Arzneimittel,
31 Pütter GmbH and Co KG, Novartis, Servier, and Shire; and has authored books and articles on ADHD
32 published by Elsevier, Hogrefe, Schattauer, Kohlhammer, Karger, and Springer.
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42 597 We used the SPIRIT checklist when writing our report ⁶⁶
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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).

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

311x93mm (300 x 300 DPI)

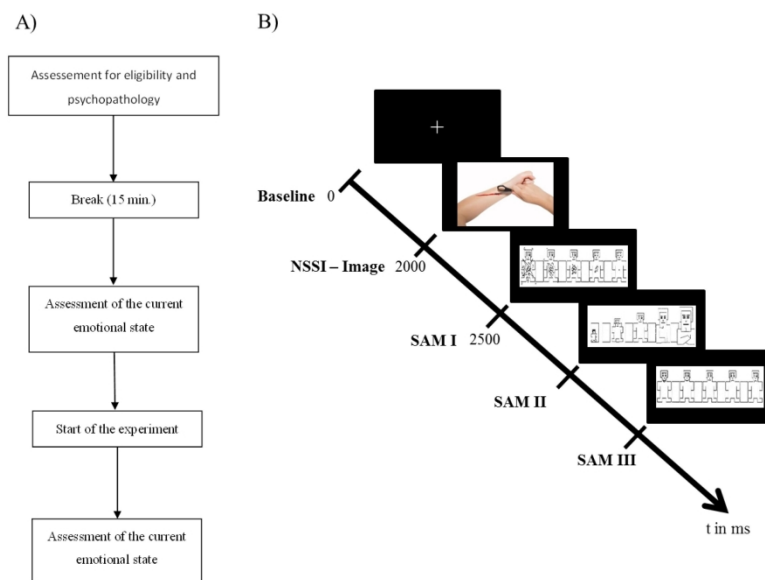


Figure 3. A) Study design. B) Experimental paradigm; NSSI=non-suicidal self-injury; SAM I/II/III=Self-Assessment Manikin (Dominance, Arousal, and Valence) presented pseudorandomized

311x196mm (300 x 300 DPI)

BMJ Open

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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Primary Subject Heading:	Medical publishing and peer review
Secondary Subject Heading:	Mental health
Keywords:	Borderline, Emotion regulation, Emotional stimuli, NSSI

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Manuscripts

1 Development and validation of an 2 emotional picture set of self-injury 3 (EPSI) for borderline personality 4 disorder: protocol for a validation study

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48 **Abstract**

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

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

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

63 **Trial registration number:** clinicaltrials.gov: NCT03149926

64 **Keywords:** Borderline, Emotion regulation, Emotional stimuli, NSSI

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3 74 **Strengths and limitations of this study**
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- 5 75 • Controlled study design to develop emotional stimuli relevant for BPD
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7 76 • Emotional reaction is assessed by subjective as well as objective measurements
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9 77 • Emotion evocation is limited to NSSI however other emotional trigger (e.g. social
10 78 interaction) are not investigated
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12 79 • Limited to BPD patients that actually engage in NSSI
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81 Introduction

82 Borderline personality disorder (BPD) is a severe psychiatric disorder that is characterized by
83 impairments in interpersonal, cognitive and emotional functioning^{1,2}. Pervasive problems of affect
84 regulation have been identified as the central dysfunction in BPD and it has been conceptualized as
85 a disorder of the emotion regulation system³. Emotion dysregulation comprises high emotional
86 vulnerability in conjunction with an inability to regulate emotions. Emotional vulnerability in
87 individuals with BPD is characterized by high sensitivity to emotional stimuli, unusual emotional
88 intensity and a slow return to emotional baseline (emotions are long-lasting). In addition, the
89 identification, expression and inhibition of emotions are impaired³⁻⁵.

90 Not surprisingly, emotionally evocative material is commonly used to investigate BPD pathology.
91 Previous studies have employed various emotional stimuli such as emotional facial expression^{6,7},
92 pleasant or unpleasant pictures^{8,9}, pictures and video clips depicting social interactions^{10,11}, or
93 script-driven imagery of a self-injurious act¹². However, extant research utilizing such emotionally
94 evocative materials are inconsistent in their ability to provoke emotional responses in BPD patients
95^{13,14}. While some studies did not find evidence for abnormal emotional responsiveness in BPD^{9,15,16}
96 others did^{12,17,18}. One possible explanation for these contradictory results might be that the stimulus
97 material was not specific enough to elicit an emotional response in participants with BPD. For
98 example, a recent study investigated differences in emotional response and specificity of the
99 presented stimuli, as well as baseline emotional intensity and emotional reactivity in BPD patients,
100 compared to healthy controls. Emotional response to six discrete emotion-eliciting film clips was
101 evaluated by measuring physiological and subjective reactions. Furthermore, the two groups were
102 compared regarding their emotional reaction to films with BPD-specific content (e.g. sexual abuse,
103 emotional dependence and abandonment/separation). Compared to healthy controls, participants
104 with BPD showed a significantly stronger emotional response to 'BPD-specific content' films¹⁸,
105 compared to films with non-BPD-specific emotional content. These findings suggest that measuring
106 emotional responses characteristic of BPD only make sense in contexts that are psychologically
107 challenging^{9,13}. The actual emergence and intensity of emotions depend on an array of psychological
108 characteristics such as personality, learning experiences and cognition, the situational context, but
109 also on the type and intensity of the perceived stimulus¹⁹. Emotional stimuli that activate specific,
110 self-relevant information seem to arouse a more intense emotional reaction than more general
111 emotional stimuli^{5,20}. Therefore, to elicit a distinctive and BPD-specific emotional response, the
112 stimulus material needs to have a high relevance for persons with BPD and needs to trigger

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3 113 sensitivities that relate to BPD⁵⁻⁹. Such a BPD specific event could include the presentation of
4 114 material used for non-suicidal self-injury (NSSI).

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7 115 NSSI is associated with clinical and functional impairments and occurs in a variety of psychiatric
8 116 disorders²¹. There is an ongoing scientific debate regarding the conceptualization and diagnostic
9 117 organization of NSSI. The fifth version of the Diagnostic and Statistical Manual of Mental Disorders
10 118 (DSM-5) presents Non-Suicidal Self-Injury Disorder (NSSID) as a separate nosological entity, but
11 119 only as a condition that still requires further investigation²¹⁻²². Thus, NSSI is not unique to BPD.
12 120 Nevertheless, there is a general consensus that NSSI is related to BPD and is considered to be a core
13 121 symptom of the disorder¹⁻²¹. NSSI is defined as a deliberate, albeit non-suicidal destruction of
14 122 healthy body tissue, in which approximately 90% of BPD patients partake²³. NSSI typically
15 123 includes repeated behaviors, such as skin cutting, banging or hitting, burning, scratching and
16 124 interfering with wound healing²⁴. Further, emotion dysregulation is closely related to NSSI in
17 125 persons with BPD. According to the experiential avoidance model, NSSI is applied to reduce or
18 126 remove aversive emotional experiences and might be maintained by negative reinforcement²⁵⁻²⁷.

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27 127 Empirical evidence suggests that NSSI is commonly performed as an emotion regulation strategy.
28 128 Self-injurers use NSSI to reduce unpleasant feelings, overcome dissociation, for self-punishment or
29 129 for the reduction of aversive inner tension²⁸⁻²⁹. Typically, NSSI is preceded by high arousal of
30 130 negative emotions, NSSI behavior is then initiated to decrease these emotions²⁹⁻³⁰. For example, a
31 131 decrease in negative affect and arousal was observed in self-injurers who were asked to visualize
32 132 cutting or to engage in another painful behavior, whereas the performance of a non-NSSI-related
33 133 task did not lead to a decrease²⁹. In addition, seeing blood during NSSI seems to be an important
34 134 aspect for many self-injurers. Glenn and Klonsky³¹ investigated the role of seeing blood during NSSI
35 135 in persons with a history of NSSI. Most participants (51.6%) reported that seeing blood during NSSI
36 136 was important. Furthermore, participants reported that seeing blood fulfilled multiple functions,
37 137 such as to relieve tension (84.8%), to calm down (72.7%), to feel real (51.5%), to show the realness
38 138 of NSSI (42.4%), to help focus (33.3%) and to show that NSSI has been performed correctly/deep
39 139 enough (15.2%). A pilot study by Naoum, et al.³² compared 20 female BPD patients and 20 healthy
40 140 controls (HC) to investigate the effect of seeing blood during NSSI following stress and pain
41 141 induction. The BPD patients demonstrated a significantly stronger decrease in arousal compared to
42 142 the HC group however, with no significant differences between blood and non-blood conditions. In
43 143 addition, the urge for NSSI was associated with a significantly greater decrease in arousal in the
44 144 blood condition in BPD patients. Yet, seeing blood did not result in greater relief of tension.

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3 145 Despite the connection between emotion regulation deficits and NSSI in BPD, there are currently no
4 146 studies utilizing stimuli depicting the varying stages of NSSI. Doing so would help investigate
5 147 whether emotional reactions in BPD patients gradually depends on the stage of NSSI presented by
6 148 the stimuli. Thus, a specified stimuli-database, validated in a BPD population for evoking emotional
7 149 responses in BPD is lacking.

11 12 150 **This Study**

13 151 Although emotion dysregulation is recognized as a core symptom of BPD, current evidence is
14 152 inconsistent and contradictory. This could be explained, at least partially, by the use of unsuitable
15 153 and unspecific emotional stimuli that do not tap into BPD-relevant themes. However, to improve
16 154 and extend research on emotion regulation in BPD, the availability of validated emotional stimuli,
17 155 that reliably elicit emotional reactions specifically for BPD, is a necessary prerequisite.

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22 156 This study aims to develop and validate an emotional picture set, EPSI (emotional picture set with
23 157 scenes of self-injury), relevant for BPD. In a second step, emotional reactions will be assessed by
24 158 means of a self-report measurement, as well as by a psychophysiological assessment of emotional
25 159 reactions in participants with BPD who engage in NSSI, in a depressive control group and in a
26 160 sample of matched healthy controls. Furthermore, participants are asked to indicate how strong the
27 161 pictures relate to their person or biography. EPSI depicts objects frequently used for NSSI and
28 162 shows the application of these objects at different stages of NSSI (objects only, pre-NSSI and during-
29 163 NSSI). As NSSI can be associated with different emotional reactions depending on the stage of NSSI,
30 164 differences in the emotional reactions are expected for participants with BPD and their respective
31 165 NSSI stage. In the pre-NSSI stage (preparing for NSSI), negative affect, arousal and tension are
32 166 expected to be strongest. As NSSI behavior begins, negative affect, arousal and tension might start to
33 167 decrease. In the during-NSSI stage (successfully performed NSSI i.e. seeing blood), an even stronger
34 168 decrease of emotions and a sense of relief and relaxation is expected. We predict that the control
35 169 groups will show emotional reactions opposite that of BPD, that is, the control groups are expected
36 170 to show low emotional responses when seeing pictures of NSSI objects and pictures of the pre-NSSI
37 171 stage; they will show strong responses when watching pictures of the during-NSSI stage. Lastly, BPD
38 172 participants are expected to report higher self-referencing in response to the pictures when
39 173 compared to controls.

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42 174 To investigate whether our database is BPD relevant, evaluations of the NSSI images will be
43 175 compared with neutral images and with two separate control groups. In this way, the present study

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3 176 will investigate to what extent EPSI can elicit an emotional response specifically for persons with
4 177 BPD and if the emotional response differs with regard to the stage of NSSI.

7 178 **Objectives**

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9 179 The primary outcome variables include self-rated emotional reactions, as measured by the Self-
10 180 Assessment-Manikin (SAM) ³³; psychophysiological parameters of emotional reactions will be
11 181 assessed using heart rate variability (HRV), as an indicator of autonomic nervous system (ANS)
12 182 activity. Finally, facial expressions will be analyzed and measured with the Noldus FaceReader
13 183 software (Noldus Information Technology, www.noldus.com). As a secondary outcome variable,
14 184 self-reference of EPSI will be measured on a 5-point Likert-scale, using the item 'How much do you
15 185 see a relation to your own person/to your biography?' from 1 (not at all) to 5 (very much) ¹⁸.

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21 186 Primary objectives:

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23 187 1. An NSSI image database will be created (EPSI) to develop a BPD-relevant stimulus set.
24 188 2. A within-groups comparison of emotional reactions to EPSI and neutral stimuli will be
25 189 conducted to validate EPSI. Moreover, the emotional reactions to EPSI will be compared
26 190 amongst patients with BPD, depressed patients and healthy controls.

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31 191 Secondary objectives:

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33 192 1. To assess how emotional reactions in participants with BPD, who engage in NSSI, gradually
34 193 depend on seeing NSSI objects, pre-NSSI pictures and during NSSI pictures.
35 194 2. To investigate if participants with BPD who engage in NSSI rate EPSI as more self-referential
36 195 than matched healthy controls and depressive controls.
37 196 3. To determine if self-referential measurement correlates positively with the actual emotional
38 197 response.
39 198 4. To assess if BPD symptomatology correlates positively with emotional responses.
40 199 5. To investigate if self-rated emotional responses correlates with psychophysiological
41 200 measurements of emotional responses within and between groups.

42 43 44 45 46 47 48 49 201 **Methods and analysis**

50 51 52 202 **Participants**

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54 203 In total, 90 participants (30 BPD patients, 30 depressed patients and 30 healthy control subjects)
55 204 of 18-60 years of age will be recruited. To control for altered autonomic responses, all participants

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3 205 must be free of severe and persistent neurological disorders (in particular, epilepsy, multiple
4 206 sclerosis, stroke or neurodegenerative diseases). Participants are not allowed to be currently
5 207 medicated with antihistamines, neuroleptic medication, tranquilizers or beta blockers. Further, the
6 208 BPD patients must have a lifetime history of self-injury. Exclusion criteria for the BPD patients
7 209 include psychotic disorders, current major depressive episode and acute suicidal crisis. Patients in
8 210 the depressed control group need to have a current major depressive episode (depressive
9 211 symptoms for at least 2 weeks). Depressive patients who also meet diagnostic criteria for a
10 212 psychotic disorder will be excluded. The healthy control group must not exhibit a current
11 213 psychiatric disorder or history of self-injury. Additional exclusion criteria for both control groups
12 214 include attempted suicide or current suicidal ideation. Control groups will be matched to the BPD
13 215 group on age and sex.

21 216 ***Patient and public involvement***

22 217 Patients were not involved in the development of the research question, outcome measures or study
23 218 design.

24 219 **Diagnostic procedure**

25 220 Assessments of DSM-IV Personality Disorders (ADP-IV)^{34 35} and the Borderline Symptom Checklist
26 221 (BSL-23)³⁶ will be used to verify the diagnosis of BPD and to assess BPD symptoms. The structured
27 222 clinical interview (SCID I,II) will be performed to assess psychiatric disorders³⁷. Further, a
28 223 demographic questionnaire, as well as the Edinburgh Handedness Inventory³⁸, will be applied.

29 224 To record the history and methods of self-injury, the Inventory of Statements about Self-Injury
30 225 (ISAS) and the Self-Harm Behavior Questionnaire (SHQ) will be applied^{39 40}. Any outcome above
31 226 zero (meaning that NSSI has been performed) on the ISAS or SHQ will be an exclusion criterion.
32 227 General psychopathology will be recorded with the symptom checklist-90 (SCL-90)⁴¹. Depressive
33 228 symptoms will be self-rated with the Beck Depression Inventory (BDI)⁴². Since the study will assess
34 229 the emotional processing of images, the current mood and stress of the participants could have an
35 230 influence. Therefore, they will be asked how emotionally strained and charged they are at the
36 231 moment before and during testing, using a Likert-scale ranging from 0-10. A short break is planned
37 232 in the middle of the experiment to check on the patients' psychological distress. Acute somatic and
38 233 psychological dissociation will be assessed via the short version of the Dissociative State Scale (DSS)
39 234⁴³.

235 **Stimuli**

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

244 **Experimental Design**

245 Participants will be asked to watch the images and to rate their current emotion on scales of
246 arousal, dominance and valence, for which the Self-Assessment Manikin (SAM) will be used ⁴⁷. In
247 addition, neutral objects will be displayed to provide control images (e.g., towels, books; see Figure
248 2 for examples of neutral images), which will be taken from an existing and validated database ⁴⁸. A
249 break will be included half way through the stimulus presentation, to assess participants' emotional
250 status and to prevent dissociations ⁴⁹. Image presentation and SAM rating-screens will be
251 pseudorandomized across all categories. Medical professionals will be monitoring the participants
252 to prevent overstraining and to intervene if necessary. In total, 90 images will be shown (45 EPSI/
253 45 neutral), each for 500 ms, followed by the SAM evaluation (see Figure 3 for the study design). At
254 the end of the experiment, participants will perform a self-reference rating on all EPSI picture, using
255 a 5-point scale with anchors: 1='Not at all related to me' and 5='Definitely related to me'. See table 1
256 for study timeline flow.

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258 *-Please insert Figure 1-*

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261 **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*
262 *NSSI by BPD patients (self-injury objects; SIO), scenic presentation of usage shortly before the injury (SIO_{bi}) and scenic presentation during*
263 *the usage of SIO (SIO_{dur}).*

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265 *-Please insert Figure 2-*

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

267 **Physiological Measurement**

268 **Autonomic nervous system**

269 Heart rate variability (HRV) is a valid and reliable indicator of autonomic nervous system (ANS)
270 activity, and is a transdiagnostic marker of psychopathology^{50 51}. Heart rate will be recorded
271 continuously with an EC-12R PC-based resting ECG system (Labtech, Debrecen, Hungary). Three
272 electrodes will be attached according to Einthoven's triangle and a ground at the right lower limb⁵².
273 To derive HRV, a frequency domain analysis will be conducted by taking a Fourier transformed
274 time-domain representation of the inter-beat-interval (IBI)⁵³. Since we plan to record task-
275 concurrent HR, the low (LF; 0.04-0.15 Hz) and high (HF; 0.15-0.4 Hz) frequency bands will be of
276 particular interest,⁵⁴. The HRV-data will be processed with the Kubios HRV software
277 (www.kubios.com)⁵⁵. A threshold-based artifact correction algorithm, as it is implemented in the
278 Kubios software, will be performed. To separate ectopic and misplaced beats from the normal sinus
279 rhythm, the automatic artifact correction algorithm will be used⁵⁵. Further, heart rate reactivity will
280 be calculated.

281 **Emotional face activation**

282 The universal emotions of happy, sad, angry, surprised, scared, disgusted, and neutral, as proposed
283 by Ekman⁵⁶, will be measured with Noldus FaceReader software (Noldus Information Technology,
284 www.noldus.com). The program reliably detects facial expressions and was successfully applied in
285 numerous studies^{57 58}. Participants will be videotaped with a webcam throughout the session, using
286 a frame-by-frame analysis during which 500+ key points of the participant's face will be localized
287 and compared to a database of annotated images. The intensity of the universal emotions is then
288 decoded on a scale from 0 to 1, where 0 indicates an absent emotion and 1 an intense emotional
289 reaction. In addition to the universal emotions, the software also captures valence and arousal.
290 Valence is calculated by subtracting the intensity of negative expressions (angry, scared and
291 disgusted) from the intensity of 'happy' expressions. Arousal is calculated by subtracting the mean
292 activation of specific facial muscle groups, occurring over the last 60 seconds, from current muscle
293 activation. The mean of the five highest values then yields the value of arousal.

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

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10 299 **Figure 3.** A) Study design. B) Experimental paradigm; NSSI=non-suicidal self-injury; SAM I/II/III=Self-Assessment Manikin
11 (dominance, arousal and valence) presented pseudorandomized
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13 300 **Statistical analysis**

14 15 301 **Stimulus Validation**

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18 302 Interrater reliability will be assessed with Krippendorff's alpha. The advantage of this method over
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20 303 competing methods is that Krippendorff's alpha allows for more than two raters (unlike Cohen's
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22 304 Kappa) and can handle missing data points (unlike Fleiss Kappa) ⁵⁹. The assumption of
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24 305 Krippendorff's alpha is based on the observed disagreement corrected for disagreement by chance,
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26 306 which is calculable within a range of -1 to 1, where 1 illustrates perfect agreement, 0 no agreement
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28 307 beyond chance and negative values indicate inverse agreement ⁵⁹ ⁶⁰. Bootstrapped confidence
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30 308 intervals will be used since the distribution is not known, the derivation of the correct standard
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32 309 error is not straightforward and the type 1 error level is acceptable ⁵⁹ ⁶¹ ⁶². Krippendorff's alpha will
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34 310 be computed for each SAM-dimension, for each stimuli category.

35 36 311 **Behavioral Data**

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38 312 If the data show a normal distribution, a 2x3x4 between-subjects analysis of variance (ANOVA) will
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40 313 be computed with the factors group, SAM-evaluation and stimulus category. Further, the
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42 314 questionnaire scores will be correlated with the SAM-evaluations for each stimulus category. To
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44 315 assess gender bias, a linear regression will be performed to rule out possible performance
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46 316 differences.

47 317 48 318 **Physiological Data**

49 319 **HRV**

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52 320 Group-wise comparisons of HRV will be computed with a 2x2x4 ANOVA with the factors group,
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54 321 frequencies and stimulus category.
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323 **Emotional Face Activation**

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

329 **Sample size justification**

330 Based on calculations with G*Power, a fixed effects ANOVA with 30 participants per group will yield
 331 a large effect size (0.62) with a power of 0.66⁶³. The size of the groups was derived from earlier
 332 studies comparing the affective reaction of BPD patients with healthy controls while watching
 333 images ⁶⁴⁶⁵.

334 **Table 1** Study timeline flow

Months	1 st year			2 st year				3 rd 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

336 **Ethics and dissemination**

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

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3 567 **Authors' contributions**
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5 568 KB, MS: study design, literature search, figures, writing
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7 569 PS: study design, literature search, writing, supervision
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10 570 CS: study design, supervision
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12 571 AP: study design, literature search, writing, supervision
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22

23 575 **Competing interests statement**
24

25 576 KB, MS, PS, CS declare that the research was conducted in the absence of any commercial or
26 financial relationships that could be construed as a potential conflict of interest.
27 577
28

29 578 AP declares that she served on advisory boards, gave lectures, performed phase 3 studies, or
30 received travel grants within the last 3 years from Eli Lilly and Co, Lundbeck, MEDICE Arzneimittel,
31 Pütter GmbH and Co KG, Novartis, Servier and Shire; and has authored books and articles on ADHD
32 published by Elsevier, Hogrefe, Schattauer, Kohlhammer, Karger and Springer.
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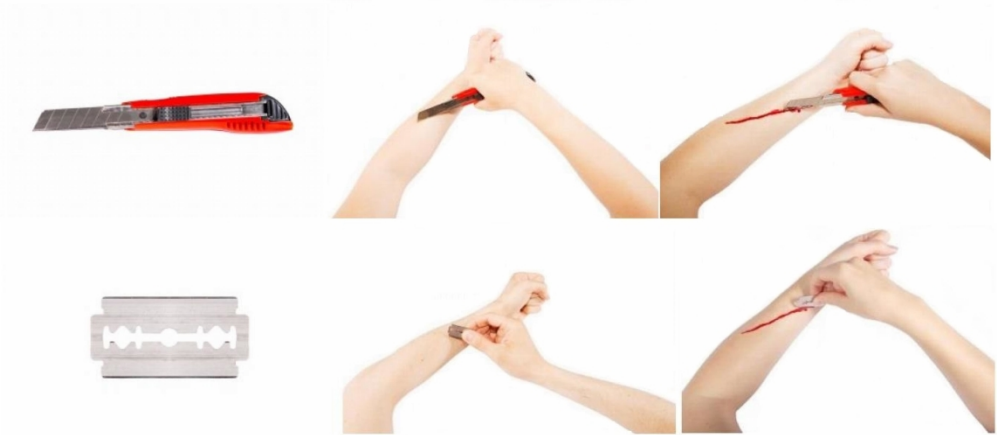


Figure 1. Examples from EPSI for the three categories of objects and scenes for NSSI. From first in a row: objects that are frequently used for NSSI by BPD patients (self-injury objects; SIO), scenic presentation of usage shortly before the injury (SIObi), and scenic presentation during the usage of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

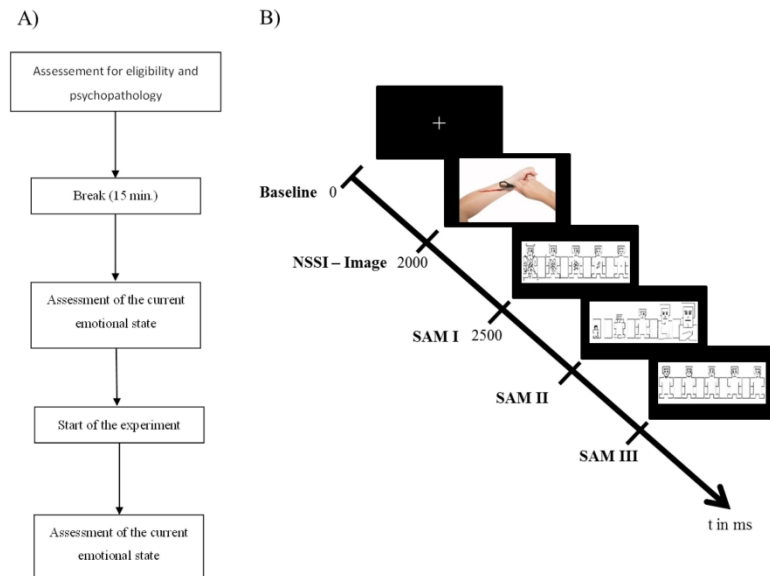


Figure 3. A) Study design. B) Experimental paradigm; NSSI=non-suicidal self-injury; SAM I/II/III=Self-Assessment Manikin (Dominance, Arousal, and Valence) presented pseudorandomized

311x196mm (300 x 300 DPI)