CRED-nf checklist summary

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Manuscript title: Amygdala-related electrical fingerprint is modulated with neurofeedback training and correlates with deep-brain activation: Proof-of-concept in borderline personality disorder
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Item No.	Checklist item	Manuscript Details
1a	Pre-register experimental protocol and planned analyses	// 2.1 Replication of Amyg-EFP-related brain pattern in Borderline Personality Disorder: The statistical analysis was preregistered before results were known (https://doi.org/10.17605/OSF.IO/KYCR6). // 2.2 Feasibility of neurofeedback training: Online preregistration: https://doi.org/10.17605/OSF.IO/6ZDS5, clinicaltrials.org: NCT03964545
1b	Justify sample size	2.2 Feasibility of neurofeedback training Online preregistration: https://doi.org/10.17605/OSF.IO/6ZDS5 : //Sample size: N=28 (N=14 per group) // Sample size rationale: A power estimate was made based on published data (Keynan et al., 2016). The authors report a statistic of T(22)=5.00 (p<0.05 FDR) for EFP-BOLD correlation in the amygdala peak voxel. Using G*Power v3.1.9.2 and assuming effect size d=1.06 in a one-sample t-test (p<0.05 two-sided), N=14 subjects are required for significance with power (1-)>0.95. This is only a rough power estimate due to lack of original data. A complementing power analysis based on comparison of amygdala (BOLD) regulation before (0.03±0.12) and after EFP NF training (-0.11±0.07; assumed correlation between measures: r=0.2; d=1.11, p<0.05) resulted in a sample size N=11 needed to achieve power>0.95 in a paired-samples t-test.
2a	Employ control group(s) or control condition(s)	2.2 Feasibility of neurofeedback training N=29 female patients diagnosed with BPD were allocated to the NF group. N=15 of them completed the study, receiving the full dose of ten Amyg-EFP NF sessions over five weeks in addition to their residential DBT treatment. N=22 female patients diagnosed with BPD were assigned to a control group, receiving no NF training in addition to DBT treatment (no-NF group).
2b	When leveraging experimental designs where a double-blind is possible, use a double-blind	*The experiment did not include a double-blind*
2c	Blind those who rate the outcomes	*Those who rated the outcome were not blind to group assignment*
	Blind those who analyse the data	*Those who analysed the data were not blind to group assignment*

This report has been generated using the CRED-nf online checklist version 1.0, adapted from the CRED-nf manuscript which is freely available here https://doi.org/10.1093/brain/awaa009.

2d	Examine to what extent participants and experimenters remain blinded	*No measures were taken to examine whether participants and experimenters remained blind*
2e	In clinical efficacy studies, employ a standard-of-care intervention group as a benchmark for improvement	*NA: This is not a clinical efficacy study*
3a	Collect data on psychosocial factors	2.1 Replication of Amyg-EFP-related brain pattern in Borderline Personality Disorder - no psychosocial information beyond inclusion criteria // 2.2 Feasibility of neurofeedback training: The two groups did not differ in clinical characteristics such as psychopathology (BSL-23, (Wolf et al., 2009)), comorbidities or psychotropic medication (Table 1). No differences were observed between the groups in baseline depression (BDI-II, (Steer et al., 1999)), anxiety (STAI, (Laux et al., 1981)), affective lability (ALS, (Harvey et al., 1989)) and alexithymia scores (TAS-26, (Taylor et al., 1985), Tables 1, 2).
3b	Report whether participants were provided with a strategy	2.1 Replication of Amyg-EFP-related brain pattern in Borderline Personality Disorder // reference dataset: During NF, participants heard a piano melody, that became louder when Amyg-EFP activation increased. In each of the 4 NF runs, they had to lower the volume of the melody by exercising mental strategies. "Instructions were intentionally unspecific, allowing individuals to adopt the mental strategy that they subjectively found most efficient" (Keynan et al., 2016, S. 491). // replication dataset: Instructions were intentionally unspecified, allowing participants to find their own mental strategy.
3c	Report the strategies participants used	*The strategies participants used were not recorded or not reported in the manuscript*
3d	Report methods used for online-data processing and artifact correction	2.1 Replication of Amyg-EFP-related brain pattern in Borderline Personality Disorder // fMRI-data used for this publication did not undergo online correction. // EEG online data processing in the reference dataset: The Amy-EFP signal was calculated online from raw EEG data using a built-in automated average artifact subtraction method implemented in BrainVision RecView (BrainProducts). RecView was custom modified to enable export of the corrected EEG data in real time through a TCP/IP socket. Preprocessing algorithm and EFP calculation models were compiled from MATLAB R2009b to Microsoft.NET in order to execute it within the BrainVision RecView EEG Recorder system. Data was then marshaled to a MATLAB.NET compiled dll that calculated the value of the EFP amplitude every 3 seconds. The online generated EFP data were used for analyses. // replication dataset: The EEG was recorded during image acquisition inside the scanner using an MRI-compatible EEG system with a 5 kHz sampling rate, 32 mV input range and 0.1–250 Hz band-pass filters. The signal was recorded by (...). The quality of the EEG was assessed during the MR-scan, using online correction software (RecView BrainProducts, Gilching, Germany).

3e	Report condition and group effects for artifacts	*Condition and group effects for artifacts were not measured, or not reported in the manuscript*
Feedback specifications		
4a	Report how the online-feature extraction was defined	*The manuscript does not report how the online-feature extraction was defined*
4b	Report and justify the reinforcement schedule	*The manuscript does not report or justify the reinforcement schedule*
4c	Report the feedback modality and content	// 2.1 Replication of Amyg-EFP-related brain pattern in Borderline Personality Disorder // reference dataset: The experimental group (N=17) received continuous feedback from the Amyg-EFP and the control group (N=7) from the alpha-theta ratio. More details can be found in the original publication (Keynan et al., 2016). During NF, participants heard a piano melody, that became louder when Amyg-EFP activation increased. // replication dataset: The simultaneous EEG-MR-scan was composed of 3 runs: a resting-state scan (6 min), a short NF run (6 min) and a long NF run (22 min), during which individuals received continuous fMRI-NF. Participants were instructed to downregulate (short NF run) a visual analogue scale illustrating brain activity or to up- and downregulate brain activity in alternating blocks (long NF run, Supplement Figure S1) using mental strategies. // 2.2 Feasibility of neurofeedback training // EFP-trainings: Participants were sitting with eyes open in a relaxed position in front of a black computer screen. A piano melody of 3 seconds was repeatedly played to participants (Kinreich et al., 2014). Participants were instructed to downregulate the volume. (..) Every cycle was composed of a baseline block of 1 minute followed by a feedback block of 3 minutes. The audio volume was adjusted to the meas
		ured Amyg-EFP signal in feedback blocks and was fixed at 70% of the maximum volume in baseline blocks. Participants reached the minimum/maximum volume when the Amyg-EFP signal was < -2 SD/>2SD from the preceding baseline mean (baseline values of the initial 6s were dropped).

4d	Collect and report all brain activity variable(s) and/or contrasts used for feedback, as displayed to experimental participants	// 2.1 Replication of Amyg-EFP-related brain pattern in Borderline Personality Disorder: see original publicatioin about Amyg-EFP. From this manuscript's introduction: To overcome the limited anatomical specificity of EEG, the Amyg-EFP has been developed based on simultaneously acquired fMRI and EEG. Machine learning was used to predict the amygdala Blood Oxygenation Level Dependent (BOLD) signal from time and frequency information from band-widths recorded with three scalp EEG-electrodes: ground, reference and one more electrode (Figure 1). The resulting signal is an EEG surrogate of BOLD activation, optimized for the amygdala. The Amyg-EFP was validated in an independent sample to prove its usefulness as a generic feedback signal, that is: Patients do not require an individual EEG-fMRI session, as the Amyg-EFP algorithm is expected to reliably correlate with the amygdala BOLD signal across participants (Meir-Hasson et al., 2016). // 2.2 Feasibility of neurofeedback training - EFP-trainings: The audio volume was adjusted to the measured Amyg-EFP signal in feedback blocks and was fixed at 70% of the maximum volume in baseline blocks. Participants reached the minimum/maximum volume when the Amyg-EFP signal was < -2 SD/>2SD from the preceding baseline mean (baseline values of the initial 6s were dropped).
4e	Report the hardware and software used	// 2.1 Replication of Amyg-EFP-related brain pattern in Borderline Personality Disorder reference dataset: // fMRI: Structural and functional scans were performed using a GE 3T Signa Excite echo speed scanner with an 8-channel head coil, and a resonant gradient echoplanar imaging system. The scanner was located at the Wohl Institute for Advanced Imaging at the Tel-Aviv Sourasky Medical Center. fMRI preprocessing and analysis: fMRI data was imported to the Brain Imaging Data Structure (BIDS) (Gorgolewski et al., 2016), using adapted code-scripts based on the Rapid, automated BIDS conversion (RaBIDS) pipeline (Paret, 2023b) , and preprocessed with fMRIPrep v20.0.6 ((Esteban et al., 2019), see Supplement). SPM12 v7771 (The Wellcome Centre for Human Neuroimaging, London UK) was used for first-level analysis. // EEG: EEG was acquired with an MR-compatible BrainAmp-MR amplifier (BrainProducts, Munich, Germany) and BrainCap electrode cap with sintered Ag/AgCl ring electrodes (30 channels, 1 ECG channel, 1 EOG channel; Falk Minow Services, Herrsching-Breitbrunn, Germany). Electrodes were positioned to 10/20 system with the reference electrode between FCz and Cz. The raw EEG was sampled at 250 Hz and recorded using Brain Vision Recorder software (Brain Products). Online calculation of Amyg-EFP: The Amy-EFP signal w

		as calculated online from raw EEG data using a built-in automated average artifact subtraction method implemented in BrainVision RecView (BrainProducts). RecView was custom modified to enable export of the corrected EEG data in real time through a TCP/IP socket. Preprocessing algorithm and EFP calculation models were compiled from MATLAB R2009b to Microsoft.NET in order to execute it within the BrainVision RecView EEG Recorder system. Data was then marshaled to a MATLAB.NET compiled dll that calculated the value of the EFP amplitude every 3 seconds. // replication dataset: // fMRI: Structural and functional scans were performed using a 3 Tesla MRI Scanner (Trio, Siemens Medical Solutions, Erlangen, Germany) with a 20-channel head coil. After the first 8 study subjects the MR-scanner received an upgrade (PRISMAfit , Siemens Medical Solutions, Erlangen, Germany) with which all remaining subjects of the study were scanned. fMRI preprocessing and analysis: Preprocessing and analysis steps were identical with the analysis of the reference dataset. Heavily movement-affected volumes were repaired, using the ArtRepair toolbox (https://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html). After re-estimating the SPM model using the repaired volumes, the improvement between the repaired and the orig
		inal model was assessed based on global quality estimates (whole-brain contrast-to-noise ratio). The re-estimated SPM model from 4 subjects was used for further analysis, as quality improved >5% relative to the original SPM model. // 2.2 Feasibility of neurofeedback training: // EFP NF-trainings: EEG was recorded with 3 electrodes: the ground (AFz), reference (FCz) and active electrode (Pz) were mounted according to the 10-10 system using a standardized cap (Easycap, Herrsching, Germany). The EEG-signal was recorded with BrainAmp ExG-amplifier (BrainProducts, Gilching, Germany) with a sampling rate of 250Hz and the following filters: Low-Cutoff= 3Hz, High-Cutoff= 70Hz and no Notch filter. Electrode impedances were kept below 5kΩ. The recording software was BrainVision Recorder (BrainProducts, Gilching, Germany). // EEG (simultaneous MR-EEG scan): The EEG was recorded during image acquisition inside the scanner using an MRI-compatible EEG system (...) (64Ch BrainCap-MR with Multitrodes; Easycap, Munich, Germany). (...) The signal was transmitted from two MRI-compatible amplifiers (BrainAmp MR,BrainProducts, Gilching, Germany) outside the scanner via optic fibers. (...) The quality of the EEG was assessed during the MR-scan, using online correction software (RecView BrainProducts, Gilching, Germany).
5a	Report neurofeedback regulation success based on the feedback signal	2.2 Feasibility of neurofeedback training Training success was quantified as the personal effect size (PES) (Paret et al., 2019). PES measures the change of the Amyg-EFP signal from a NF block (3 min; 60 samples) relative to the preceding baseline block (1 min; 20 samples) divided by the pooled standard deviation.

5b	Plot within-session and between-session regulation blocks of feedback variable(s), as well as pre-to-post resting baselines or contrasts	2.2 Feasibility of neurofeedback training PES values of each block were averaged and analyzed with multilevel regression analysis using the lme4 package (Bates et al., 2015). The model reflected the nested data structure of blocks within sessions and sessions within participants, and included a Subject random effect. To analyze the linear effect of session progression, capturing the incremental learning effect across training sessions, "Session" was included as a random effect. The random effect for the "Subject x Session" interaction was included. The fixed effect "Session" was assessed for significance. Session was centered on the first run (i.e., x centered = x-1). Data was assessed for heteroscedasticity via visual inspection of quantile-quantile plots.
5c	Statistically compare the experimental condition/group to the control condition(s)/group(s) (not only each group to baseline measures)	*The manuscript does not statistically compare the experimental condition/group to the control condition(s)/group(s)*
Outcome measures - behaviour		
6a	Include measures of clinical or behavioural significance, defined a priori, and describe whether they were reached	*The manuscript does not include measures of clinical or behavioural significance*
6b	Run correlational analyses between regulation success and behavioural outcomes	*This manuscript does not compare regulation success and behavioural outcomes*
7a	Upload all materials, analysis scripts, code, and raw data used for analyses, as well as final values, to an open access data repository, when feasible	2.3 Availability of materials Questionnaire data, individual fMRI and EEG data is available on reasonable request and can be shared in line with applicable data protection regulations. Analysis code of self-report and NF training data is openly available (Paret, 2023a). The T-map from the second-level fMRI analysis (i.e., aggregated data across subjects) is available on neurovault (https://neurovault.org/collections/JBICXOQC/) [to reviewers/editor: private collection, will be made public upon acceptance of manuscript].