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Research paper

A machine-learning approach for differentiating borderline personality disorder from community participants with brain-wide functional connectivity

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ABSTRACT

Background: Functional connectivity has garnered interest as a potential biomarker of psychiatric disorders including borderline personality disorder (BPD). However, small sample sizes and lack of within-study replications have led to divergent findings with no clear spatial foci.
Aims: Evaluate discriminative performance and generalizability of functional connectivity markers for BPD.
Method: Whole-brain fMRI resting state functional connectivity in matched subsamples of 116 BPD and 72 control individuals defined by three grouping strategies. We predicted BPD status using classifiers with repeated cross-validation based on multiscale functional connectivity within and between regions of interest (ROIs) covering the whole brain—global ROI-based network, seed-based ROI-connectivity, functional consistency, and voxel-to-voxel connectivity—and evaluated the generalizability of the classification in the left-out portion of non-matched data.
Results: Full-brain connectivity allowed classification (~70 %) of BPD patients vs. controls in matched inner cross-validation. The classification remained significant when applied to unmatched out-of-sample data (~61–70 %). Highest seed-based accuracies were in a similar range to global accuracies (~70–75 %), but spatially more specific. The most discriminative seed regions included midline, temporal and somatomotor regions. Univariate connectivity values were not predictive of BPD after multiple comparison corrections, but weak local effects coincided with the most discriminative seed-ROIs. Highest accuracies were achieved with a full clinical interview while self-report results remained at chance level.
Limitations: The accuracies vary considerably between random sub-samples of the population, global signal and covariates limiting the practical applicability.
Conclusions: Spatially distributed functional connectivity patterns are moderately predictive of BPD despite heterogeneity of the patient population.

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1. Introduction

Impaired social interactions are a central characteristic of personality disorders (Schilbach, 2016). Borderline personality disorder (BPD) has been empirically characterized by profound social deficits, with patients notably suffering from dysfunctional relationships (Fonagy and Luyten, 2009). Core clinical features of BPD include affective dysregulation (Reisch et al., 2008), impulsivity (Grootens et al., 2008), heightened risk for self-harm and suicidality (Black et al., 2004), relational instability and hypervigilance to motives of others in close relationships (Fonagy and Allison, 2014) and a bias in attributing hostility to others (Critchfield et al., 2007). The core of patients' difficulties has been suggested to lie with an inability to imagine and thus perceive and interpret human behaviour in terms of underlying mental states (Allen et al., 2008; Euler et al., 2019). These social cognitive impairments may reflect changes in the capacity to understand the internal states of self and others and respond to implicit trust gestures (Debbané and Nolte, 2019; Nolte et al., 2023). This may be particularly relevant for BPD as a developmental psychopathology, for which early adversity and disorganized attachment relationships have been established as critical contributing factors. A cascade of deteriorating disease states in patients is often provoked by heightened interpersonal stress/threat (e.g. rejection, abandonment, or isolation) accompanied by a reduced sense of agency and a resulting propensity to react (Fonagy and Luyten, 2009; Nolte et al., 2019). While there is accumulating evidence that symptoms such as emotional dysregulation are associated with functional and structural differences in frontal and limbic regions (Herpertz et al., 2018; Schulze et al., 2016), relatively few studies have examined resting state functional connectivity differences in BPD. Some studies have reported connectivity increases while others have reported seed region-specific decreases, with the overall effect sizes being small and spatially scattered (Krause-Utz and Schmahl, 2016; Lei et al., 2018; O'Neill et al., 2015; Quattrini et al., 2019; Salvador et al., 2016; Wolf, 2011). Other approaches have been proposed to evaluate brain connectivity differences, e.g. anatomical connectivity based on diffusion tensor imaging. These have suggested mainly reduced fractional anisotropy (FA) values in BPD, although the specific tracts appear to differ from study to study. One study found reduced FA values in the inferior longitudinal, uncinate and occipitofrontal fasciculi (New et al., 2013), in adolescent but not adult participants. Another study tested the fractional anisotropy (FA) only in the uncinate and cingulum, finding decreased FA values in BPD sample compared to controls in the uncinate and not in the cingulum. By contrast, two further studies did find effects in the cingulum (Goldstein et al., 2019; Ninomiya et al., 2018) and, in the case of one of the studies, not in the uncinate fasciculus (Ninomiya et al., 2018). A small meta-analysis of four studies also showed support for decreased FA values in BPD localized in the corpus callosum and the fornix (Kelleher-Unger et al., 2021). Some further studies have produced high accuracies and effect sizes based on other measures, such as BOLD power at specific frequency bands or network analysis techniques (Xu et al., 2016), but like most other studies to date, they have relied on small samples and the findings have not yet been replicated. Therefore, there is a concerning lack of consensus on whether, or in which ways, BPD may be characterized by aberrations in brain connectivity.

An important limitation of prior functional connectivity studies of BPD has been the small sample size, usually approximately 20 patients in the studies cited above, although some studies with double the number of subjects exist (Baczkowski et al., 2017; Lei et al., 2017, 2019; Shafie et al., 2023). Moreover, the lack of within-study replication through independent and repeated cross-validation has limited the insight into the reliability of the findings. To address these issues, we recruited a larger group of individuals with BPD from several referral services and a group of healthy controls (HC) in order to assess the reliability of the findings. Due to the inconclusive prior literature, we adopted an explorative approach by calculating the functional connectivity of fMRI data over the whole brain at different spatial scales and used these connectivity values as features in a machine learning classification approach. The different scales of analysis are schematically visualized in Fig. 1 using a set of illustrative regions. We evaluated the effects of spatial smoothing and global signal regression on prediction accuracies with repeated 5-fold cross-validation of balanced and matched subgroups (inner cross-validation). Finally, we evaluated the generalizability of the findings by applying the classifiers to the participants that were excluded from the matched inner cross-validation.

2. Methods and materials

2.1. Participants

One hundred and eighty-seven adult participants were selected from a larger study investigating social exchanges in BPD and antisocial personality disorder reported on elsewhere (Euler et al., 2019; Huang et al., 2020; Rifkin-Zybutz et al., 2021; Wendt et al., 2022). All participants provided a written informed consent before participating in the study. Here, we included only the control participants and the patients with BPD. From those, we excluded participants that had >10 % of their data affected by excessive motion (defined as >0.5 mm framewise displacement; $N = 17$) or whose data was otherwise noisy (extensive signal distortion in the EPI images; N = 1), and participants with incomplete data on sex/gender ($N = 2$), leaving 167 participants (63 HC, 104 BPD as reported by referring clinician) for subsequent matching and analysis. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by [Research Ethics Committee Wales, 12/WA/0283]. For more details on recruitment, diagnostic evaluation, and medication, see Supplementary Methods.

2.2. Procedure

All participants underwent a comprehensive multi-day protocol comprising behavioral paradigms, questionnaires, diagnostic and developmental interviews, the Raven's standard progressive matrices (RSPM) test of non-verbal fluid intelligence, and structural and functional (neuroeconomics-based social tasks) magnetic resonance imaging. Resting state functional connectivity data were acquired between the last task-based fMRI paradigm and multi-parameter mapping MRI sequences. The order of the task paradigms was counter-balanced to avoid potential mean differences introduced by the preceding task, although we did not expect lasting post-task connectivity differences. During the resting state scan, participants were instructed to lie still inside the scanner with their eyes open while looking at the MS Windows 2000 start screen, with the windows logo at the center. Participants were instructed to "think of whatever comes to mind and to let their mind wander". Eye tracking was used to control whether they stayed awake during the 4:30 min of data acquisition and excluded the participants whose alertness was questionable or who fell asleep.

2.3. Functional magnetic resonance imaging

Functional imaging was performed at three sites in London, United Kingdom with similar Siemens MAGNETOM Trio 3-T MRI scannners. The voxel size of data was $3.4375 \times 3.4375 \times 4$ mm^3, FOV 220 mm, 37 slices, TR 2 s, TE 25 ms, flip angle 90°. Total duration of the functional scan was 5 min (150 volumes). T1 weighted MPRAGE images (matrix size 512×448, in-plane resolution 0.4785×0.4785 mm, 192 slices, slice thickness 1 mm, TR 1200 ms, TE 2.66, inversion time 600 ms, flip angle 12°) were acquired for anatomical registration. The scanning site was used as an additional hard criterion during pairwise matching of subjects and it was added as an effect of no interest in the analyses.

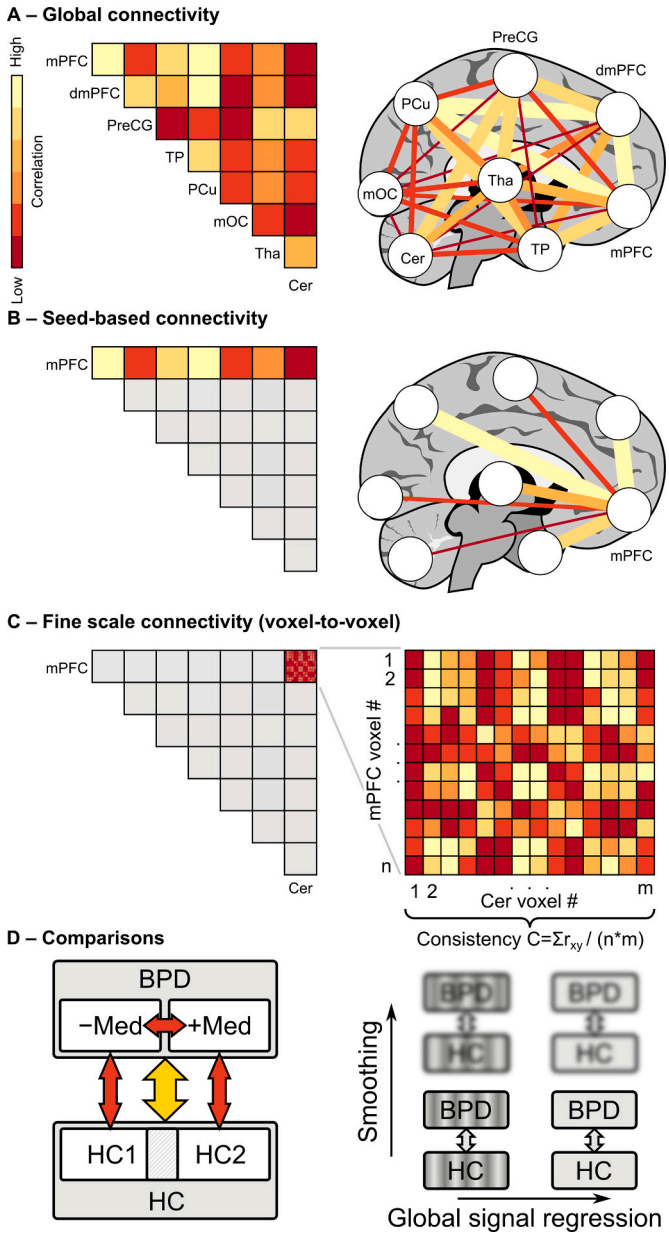

Fig. 1. Schematic representation of the scales of analysis for a selection of regions. **A** Global connectivity – The full global scale connectivity matrix between the mean time courses of each ROI was used as features for classification. **B** Seed-based connectivity – The connectivity from one ROI to all other ROIs (rows of the global connectivity matrix) are used for classification to improve spatial specificity of results. **C** Fine scale connectivity – Voxel-to-voxel connectivity between voxels in all unique pairs of ROIs are used for classification. Additionally, the consistency of ROIs and ROI pairs was calculated as the mean of all unique fine scale connectivity values. **D** Comparisons – Main comparison was between matched BPD and HC groups (left panel, yellow arrow). Additionally, to evaluate the effect of medications taken by a subset of the patient group, we repeated the global and seed-based analyses between matched groups of HC participants and sub-groups of medicated (BPD–Med) and unmedicated (BPD + Med) BPD patients as well as between the two BPD groups (red arrows). Finally, we evaluated the effects of spatial smoothing and global signal regression to the accuracies in the different analyses (right panel). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.4. Preprocessing

Standard fMRI preprocessing was performed in FSL (fMRIB Software Library; (Smith et al., 2004; Woolrich et al., 2009)) including removal of first functional volumes, motion correction, brain extraction, motion regression and blacklisting, coregistration, standardization and high-pass filtering. Additionally, effects of spatial smoothing were evaluated and a band-pass filter was applied during analysis. For additional details, see supplementary methods section.

2.5. Participant matching

The subject groups were formed using three strategies: 1 – prior referral diagnosis of BPD from referring specialist services (based upon clinical assessment by the referring clinical team from one of the seven participating London NHS Mental Health Trusts), 2 – diagnosis based on structured clinical interview according to DSM-IV performed by trained and supervised research staff (SCID II; subsequently referred to as "SCID II grouping") excluding patients who no longer filled the diagnostic criteria for BPD and control participants scoring above the cutoff in the Standardised Assessment of Personality: Abbreviated Scale (SAPAS; (Moran et al., 2003)), and 3 – cut-off on the borderline subscale of the Personality Assessment Inventory (PAI-BOR; (Morey, 1991)) measuring the self-reported symptom severity (here referred to as "PAI-BOR grouping"). In the main analysis, to be conservative and to remove variance of no interest and generate groups of comparable size, each HC participant was individually matched with a BPD participant. For details on the matching procedure and characteristics of the included samples, see Supplementary Methods.

2.6. fMRI data analysis

Data were analyzed in Matlab (R2017a; MathWorks, Inc., Natick, MA, USA). Data were loaded using NIfTI tools for Matlab (Jimmy Shen; http://de.mathworks.com/matlabcentral/fileexchange/8797-tools-for-nifti-and-analyze-image). We used "Brainnetome" (Fan et al., 2016) and probabilistic cerebellar (Diedrichsen et al., 2009, 2011) atlases masked based on voxel intensity over participants to define 273 ROIs covering the gray matter in the cerebrum and cerebellum. ROI time courses were calculated as the mean of the voxel time courses (and first principal components; see Supplementary methods). Connectivity matrices were calculated as linear correlations between ROI time courses while controlling, through linear regression, for volumes that were affected by excessive motion (FSL motion outliers output file). The analyses were repeated after regressing out the mean signal over all brain voxels to evaluate the effects of global signal regression (GSR).

We used linear support vector machine (SVM) classifiers with 5-fold cross-validation implemented in Statistics and Machine Learning Toolbox in Matlab. Classifiers were trained on data at multiple scales (see Fig. 1): 1 – the full correlation matrices (global network classification), 2 – the rows of the correlation matrices (seed based classification), 3 – mean correlation between voxels in a ROI (ROI consistency) and between ROI-pairs, 4 – full correlation matrices between voxels within ROIs (within ROI connectivity) and 5– correlation matrices between voxels of pairs of different ROIs (between-ROI connectivity). For the global network classification, we additionally performed a three-group classification using a combination of three one-class SVM classifiers (radial basis function kernel) to visualize the confusion between healthy controls and patients with and without medication. We evaluated the generalizability of effects global and local effects in left out samples. All statistics are based on repeating the analysis pipelines with permuted class labels. For more details on analyses and statistics, see Supplementary Methods.

3. Results

At the level of single links between ROIs (correlation between ROI time courses; t-test) and fine-scale connectivity (Supplementary Results), there were no significant differences with any of the group definition strategies or preprocessing approaches after correcting for multiple comparisons. Applying the global signal regression, the connectivity values were reduced leading to more negative correlations, but the group differences remained non-significant. Because the group differences did not survive corrections for multiple comparisons, we evaluated the reproducibility of local link-level differences at a more liberal threshold by repeatedly (100 iterations) splitting the data to non-overlapping discovery and replication subsamples and evaluating the replication rates (Fig. 2). No effects replicated at even moderately conservative uncorrected thresholds ($p < 0.001$; Fig. 2A, replication percentages shown black outline next to the vertical p-value thresholds). Even at liberal thresholds ($p < 0.05$, uncorrected) replication rates remained low (6.1 % for positive, 8.6 % for negative effects). However, the effects tended toward the same direction in discovery and replications subsamples as evidenced by the shift in the distributions and the lower reversal (percentages without outline) than replication rates. While replication rate across all links was relatively low, a subset of links replicated in up to 38 % of all iterations (Fig. 2B), in a sparse pattern across the brain. Fig. 2C shows the number of significantly replicable links originating at each ROI highlighting a mix of temporal, temporo-parietal, midline and subcortical regions as the most discriminative "hubs", showing the highest number of discriminative links.

Fig. 3 A shows the accuracy distributions of cross-validated support-vector machine classifiers (1000 iterations; 5-fold cross-validation within iterations) at the level of global connectivity structure compared to random permutations. Highest classification accuracies were achieved with SCID II grouping (mean accuracy 70 %, $p < 0.00001$) followed by referral diagnosis (mean accuracy ~58 %, $p < 0.05$). This drop in accuracy was driven by chance level prediction of individuals who either no longer fulfilled the diagnostic criteria for BPD in the SCID II interview (patients) or scored above threshold in the SAPAS screening questionnaire for personality disorders (controls). Accuracies using self-reported symptom severity (PAI-BOR) remained at chance level (~56 %, p ~ 0.07–0.11, n.s.). Thus, in the following figures, we will focus mainly on the SCID II grouping strategy.

Global signal regression reduced accuracies with all grouping strategies (SCID II 65 %, $p < 0.001$; referral diagnosis 55 %; n.s., PAI-BOR ~53 %, n.s). Spatial smoothing had no discernible effect on the accuracies on ROI-scale. On average, the predictive performance was largely balanced, i.e. the mean sensitivity and specificity were approximately equal to each other and to the mean accuracy.

The seed-based ROI–ROI connectivity (Fig. 3 B) revealed widely distributed areas whose connectivity profiles were predictive of BPD diagnosis with the most discriminative SCID II grouping strategy. The most discriminative regions largely overlap with social brain networks that are activated during mentalizing (Gallagher et al., 2000) extending to the left-hemisphere dominant temporo-frontal language and the intraparietal sulcus (IPS), supplementary motor area and premotor regions that are important for action understanding as well as pain perception during naturalistic social observation (Lahnakoski et al., 2012). To compare the most discriminative regions across all three grouping strategies, Fig. 3 C shows the overlap of the significantly predictive seed regions. The regions that most consistently discriminate between patients and controls with all grouping strategies include the dorsomedial prefrontal cortex, precuneus and posterior cingulate cortex, anterior temporal lobe, and left-lateralized posterior superior temporal sulcus, inferior frontal gyrus, anterior insula and supplementary motor area/paracentral lobule. The seed ROIs that reached a significant classification accuracy with at least two of the three group definition strategies are listed in Supplementary Table 2 including the top rated "Behavioral domains" listed in the Brainnetome atlas. Most common high-level domains are *cognition* (13 regions; most common sub domains were *social cognition*, *memory* and *language*, each mentioned 3 times), *perception* (8 regions, 6 of which were *visual*), *action* (4 regions including *execution*, *inhibition* and *imagination*), followed by *emotion* and *interoception* (2 regions each). The full list of significant classification accuracies with each group definition strategy and the MNI coordinates of ROI centroids and atlas labels are listed in Supplementary Table 3).

To evaluate the generalization of the findings, we applied the classifiers trained on balanced subsamples of the data to the unbalanced left out participants. Fig. 4A shows the inner and outer cross-validation

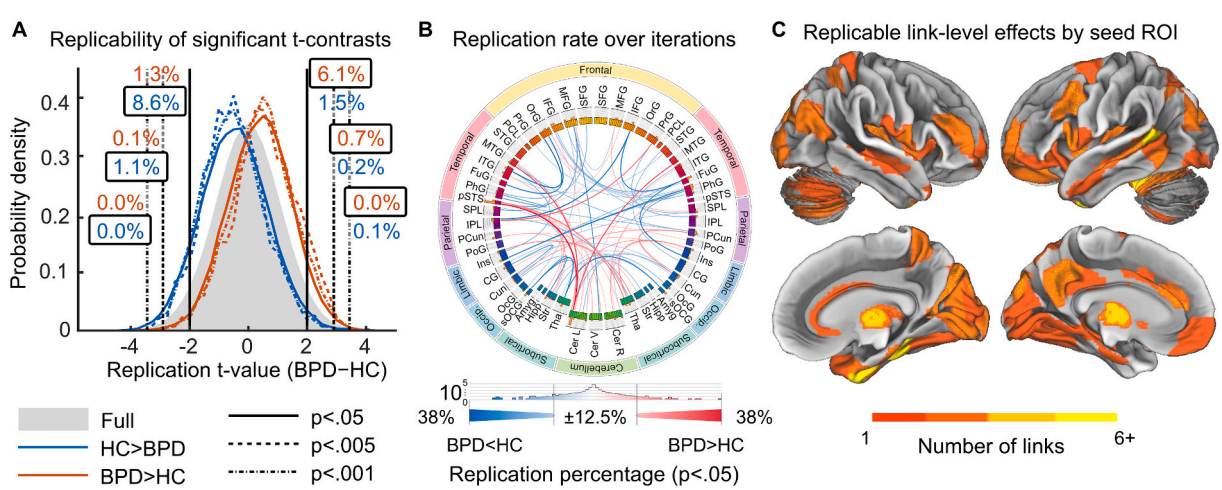

Fig. 2. Reproducibility of local differences. **A** The distribution of all local difference t-values across connections and iterations is shown in gray. The distributions of t-values in the outer cross-validation of those links that showed significant positive (BPD > HC) or negative (HC > BPD) effects in the inner cross-validation sample are shown in red and blue, respectively. The distributions and the associated (one-tailed) t-value thresholds for three p-levels are plotted in solid ($p < 0.05$), dashed ($p < 0.005$) and dot-dashed ($p < 0.001$) lines. Replication rates are shown surrounded by a black outline next to the lines denoting each p-value threshold (red numbers indicate BPD > HC and blue numbers HC > BPD effects in the discovery sample). Reversal rates of the effects are shown similarly, except without a black outline. **B** Replication rates of individual links at initial uncorrected threshold of $p < 0.05$ between discovery and replication analysis. Thickness and colour intensity indicate the percentage of replications over iterations and threshold for visualization is based on the maximum value observed in identical analysis with randomly permuted labels. Colors are similar to panel A. The distribution of replicabilities over all links is shown on a logarithmic scale below the connectivity plot. **C** Number of links showing replicable effects from each ROI (node degree in panel B). Colormap is capped at 6 to visualize differences between ROIs. However, highest observed node degree is 11 at the left pSTS ROI. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

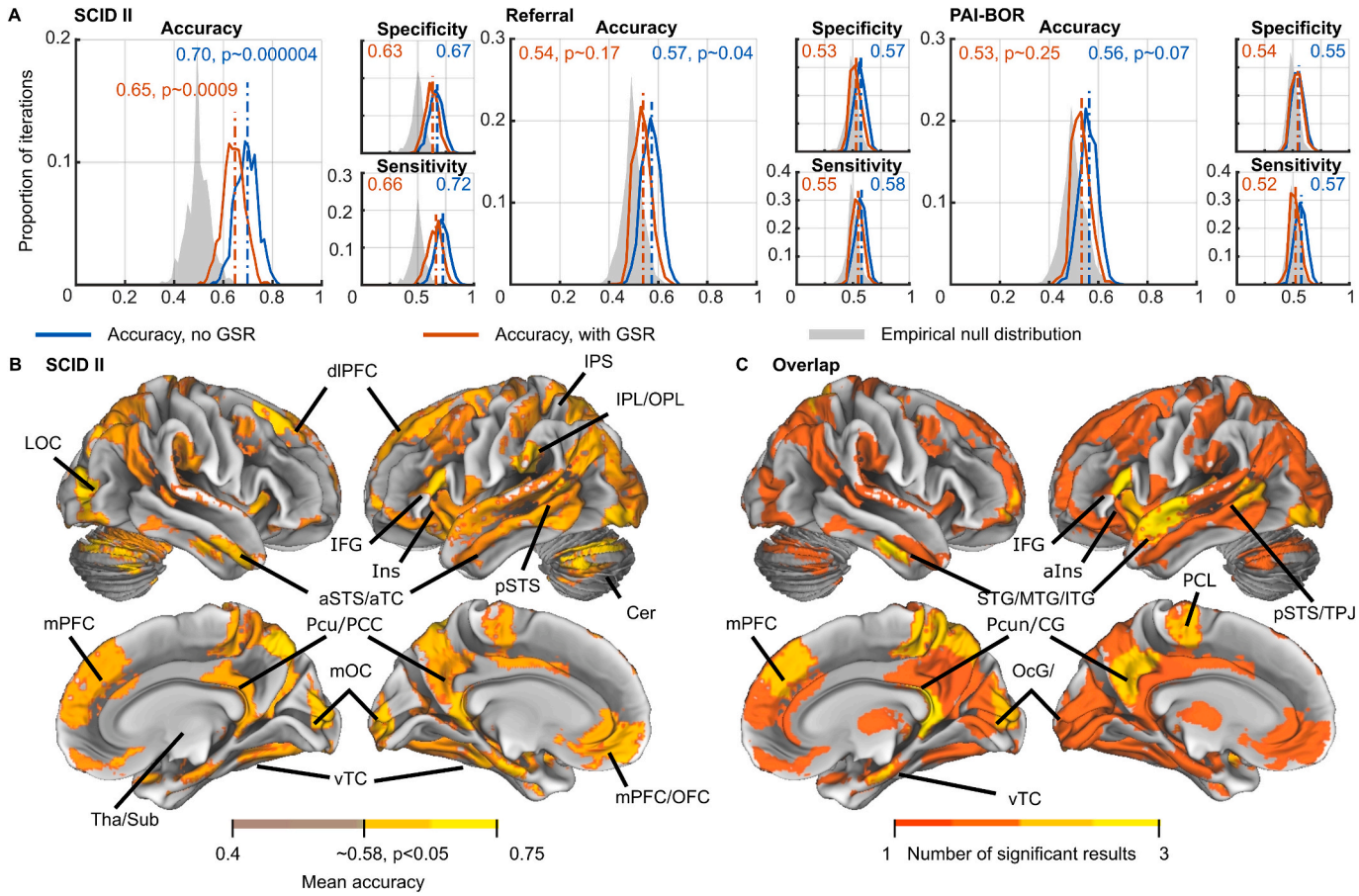

Fig. 3. Classification accuracies based on global network and seed-based ROI connectivity. **A** Distributions of accuracies based on full global network connectivity between ROIs over 1000 iterations with different group definition strategies (left – SCID II diagnosis, middle – referral diagnosis, right – PAI-BOR self-report cutoff) showing highest accuracies for the SCID II diagnosis, reduced accuracies for the referral diagnosis grouping and null accuracies for grouping based on self-reports. Null distribution using randomly permuted labels is shown in gray; accuracies without global signal regression are shown in blue and accuracies with global signal regression in red. Global signal regression reduces accuracies in all cases, but results are unaffected by spatial smoothing at the ROI scale. **B** Mean seed based accuracies visualized on the brain surface at each seed ROI location for SCID II diagnosis. Threshold is set at $p < 0.05$ in the full distribution without averaging. **C** Overlap of significantly predicting regions with the three grouping strategies. Colour indicates in how many (out of three) analyses the prediction accuracy is significant. Abbreviations: aSTS/ATC – anterior superior temporal sulcus/anterior temporal cortex, Cer – Cerebellum, IPL/OPL – inferior/opercular parietal lobule, IPS – intraparietal sulcus, LOC – lateral occipital cortex/complex, mOC – medial occipital cortex, mPFC – medial prefrontal cortex, OFC – orbitofrontal cortex, PreCG – precentral gyrus, pSTS – posterior superior temporal sulcus, TPJ – temporoparietal junction, vTC – ventral temporal cortex. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

accuracies with the different grouping strategies before (left) and after (right) removing nuisance covariates based on the training data. The colors of the dots indicate the size of the groups in the inner cross-validation sample. Although the classification accuracy remains above chance level in the outer generalization sample, the inner cross-validation tends to over-estimate the accuracy, particularly when the nuisance covariates are regressed out of the connectivity matrices.

Although the accuracies were significant, generalizable and relatively stable with multiple training sample sizes (0.6–0.7, depending on the specific approach), the real-world applicability depends on the base rate of the condition in the population. To illustrate this, Fig. 4B shows the accuracy and the positive and negative predictive values sampled at different prevalence levels in the outer cross-validation sample. While the accuracy remains stable at all prevalence levels, the positive predictive value drops (and negative value increases) quickly as the prevalence drops to more realistic levels.

Fig. 4C and D show the ROIs whose connectivity profile (rows of the connectivity matrix) was significantly predictive of BPD diagnosis using the SCID II grouping. The data are visualized as percentage of iterations where both inner and outer cross-validation results were significant (Fig. 4C) and percentage of iterations where either inner (red: Fig. 4D) or outer (blue) cross-validation accuracies were significant ($p < 0.05$, FWER controlled). The areas are largely consistent with both approaches and coincide with regions implicated in the main analysis. Additionally, we evaluated effects of symptom dimensions, medication, in-scanner motion and other confounds (see Supplementary Results). While medication affected accuracies and showed a potential interaction effect with the global BOLD signal, none of these variables contributed clearly to the observed classification accuracies above and symptom dimensions did not correlate with classifier scores beyond the mean group difference.

4. Discussion

Our study is the largest to date to assess resting state connectivity in BPD patients with a comprehensive description of patients' characteristics. Our results demonstrate that significant and wide-spread differences of functional connectivity exist in patients with borderline personality disorder compared with healthy control participants at multiple scales. By contrast, we observed no strong local univariate differences in connectivity, although some weak effects could be replicated in multiple non-overlapping subsamples. Importantly, our findings underline that a thorough diagnostic procedure based on a

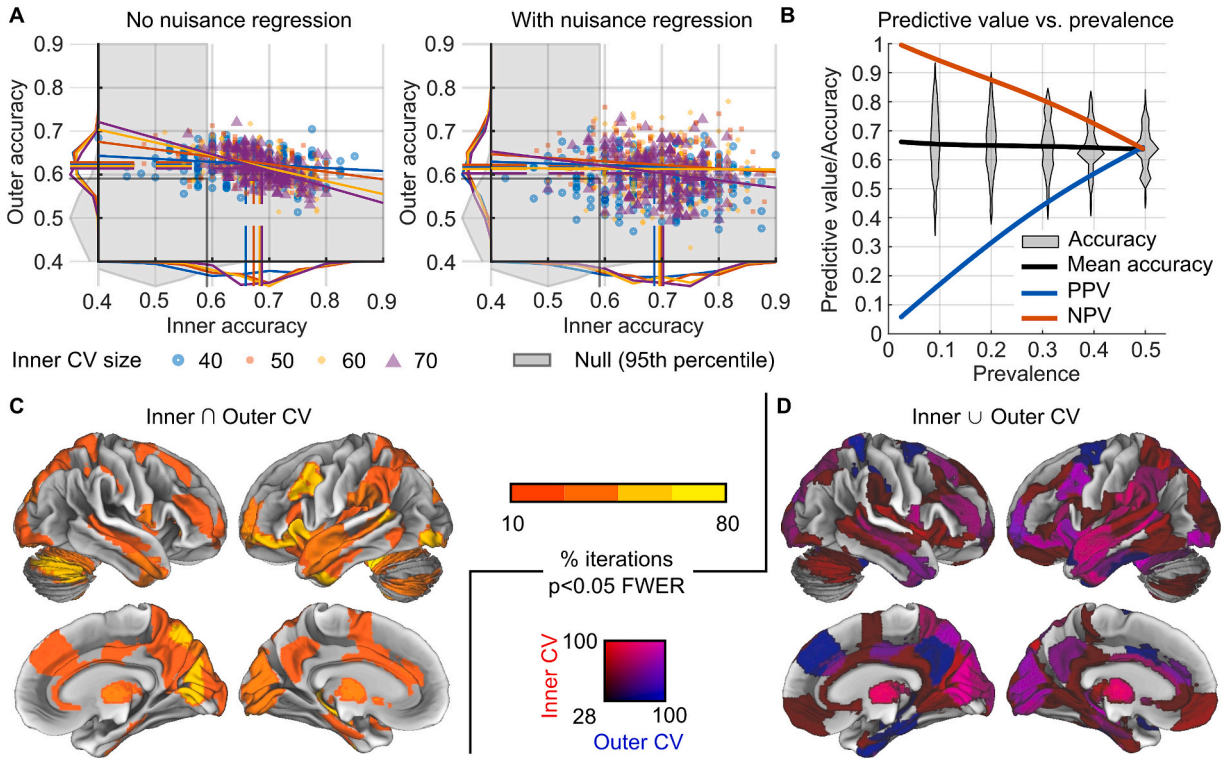

Fig. 4. Generalization of classification to unseen data. **A** Distributions of classifier performance in inner vs. outer cross-validation samples in the same iterations. Left panel shows results without nuisance regressors and right panel shows results when nuisance effects were estimated in the whole inner cross-validations sample. **B** Effects of prevalence of BPD diagnosis in the outer cross-validation sample. The mean accuracies, positive predictive values and negative predictive values are plotted against the proportion of patients in randomly selected subsets of the left-out data. **C** ROIs whose connectivity profiles significantly ($p < 0.05$, FWER controlled in empirical null analyses) predicted BPD diagnosis in both inner and outer cross-validation in the same iteration. **D** ROIs whose connectivity profiles significantly ($p < 0.05$, FWER) predicted BPD diagnosis either in the inner (red) or outer (blue) cross-validation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

structured clinical interview as well as a screening for personality disorders in the control group are associated with better discriminative performance in classification of patients. Clinically, our findings suggest that rsMRI may be sensitive to central aspects of psychopathology of BPD, although the discriminative performance is modest. Additional work should be undertaken to evaluate whether data-driven classification schemes could predict outcome and treatment assignment in the future, as is already starting to be done for other psychopathologies (e.g. (Dichter et al., 2015; Plitt et al., 2015; Whitfield-Gabrieli et al., 2015)).

Taken together, our multi-scale analyses indicate that the predictive power of functional connectivity is modest, but it is most consistent in cortical midline structures, posterior and anterior aspects of the superior temporal sulcus, and lateral parietal regions. Critically, these regions overlap with multiple different canonical functional networks that are associated with mentalizing and social processing, sensorimotor functions, action observation and bodily sensations/homeostatic monitoring. The former set of regions has recently been shown to increase in gray matter volume as a result of BPD-tailored psychotherapy (Mancke et al., 2018). Prior findings on symptom-related alterations of connectivity in BPD have been rare and reported effects relatively small. This is also consistent with the lack of robust differences of connectivity using univariate contrasts in the current data. A recent study found differences between BPD and HC individuals in degree centrality and fractional amplitude of low-frequency fluctuations in left posterior temporal lobe and precuneus, similar to the current data, and found the changes to be correlated with attachment scores in the patient population (Lei et al., 2018). Here, for the first time we used a differentiation of self-reported BPD and depression symptoms and medication status as predictors of classifier group likelihoods to assess their importance for classification. We observed no linear effects of the symptom scores beyond a mean group difference with the current symptom measures and sample size. Thus, the self-report questionnaires of symptoms appeared to be unreliable predictors of abnormal brain function and should be complemented by thorough clinician-based diagnostic procedures and quantitative interaction-based phenotyping in larger samples (Lahnakoski et al., 2022; Schilbach, 2019).

While we consistently observed significant accuracies based on widespread connectivity patterns, we observed no significant univariate group differences in the link strengths after correcting for multiple comparisons. Modestly discriminative links co-occurred with the most discriminative seed ROIs in the classification analysis. Thus, the classification performance at larger spatial scales is likely driven by distributed patterns of small, moderately replicable connectivity differences. However, the lack of strong link-level effects or information on causal direction of functional connections limits the interpretability of the connectivity differences between groups. Moreover, the accuracies achieved with the connectivity-based machine learning approach varied relatively widely (from ~40 to over 90 % in extreme cases) between repeated iterations of the same analysis pipeline with random group splits. This underlines the heterogeneity of the population (there are effectively over 120 permissible symptom combinations, which would qualify for a DSM-based clinical diagnosis; (Herbort et al., 2016)) and suggests that multiple classifications with random group splits are crucial for estimating the true expected accuracy in machine learning resting state analyses. To evaluate the generalizability of our classifiers, we applied the classifiers trained on balanced subsets to the unseen, left out participants. These results were largely consistent with those attained in the smaller matched samples, but the accuracies were inflated by nuisance regression in the inner cross-validation compared to the left-out sample. Moreover, when the inner cross-validation sizes

increased, we observed a negative correlation of inner vs. outer cross-validation accuracies as the outer cross-validation sample was increasingly constrained and imbalances between participant samples were exacerbated by the limited left-out sample size (Fig. 4A). While repeated cross-validation helps in avoiding focusing on the peculiarities of a single group split, larger samples with entirely independent replication data should be preferred in future studies. Moreover, while the current results are promising, their applicability to cross-sectional data with realistic prevalence of BPD is very limited; when prevalence is low, the positive predictive power drops drastically (Fig. 4B). Thus, significant advances are still required for clinical applications.

Global signal regression has raised considerable controversy, particularly in the field of resting state functional connectivity (Murphy and Fox, 2017). It has been argued to reflect confounding artifacts of motion and physiology, yet, regressing out the global signal also mathematically induces negative correlations in the data (Murphy and Fox, 2017). In the current study, global signal regression generally reduced accuracies, however, the effect was small, and it was even reversed when only non-medicated patients were classified against healthy controls. Thus, spatially specific effects of the global signal may affect the discriminative power of resting state functional connectivity. Spatially distinct patterns of brain regions contributing to the global signal were also shown to be predictive of schizophrenia (Yang et al., 2016). In the current study, we excluded participants with excessive motion, and controlled for signals induced by motion, white matter and cerebrospinal fluid to combat artefactual global signal changes. However, linear regression strategies do not perfectly remove all traces of these signals and they may still affect multivariate classification results. Therefore, the specific contributions of motion, cardiac and breathing rhythms and brain signals of interest should still be explored further in the future.

The reason for observing higher accuracies for the "gold standard" SCID II grouping strategy could be explained by real differences in brain connectivity in the excluded participants or mere technical issues due to different group sizes. To evaluate these options, we explored the classifier scores for the participants who were included in the Referral grouping, but were excluded from the SCID II grouping, because the groupings were in other ways equivalent. The participants were excluded due to either not meeting diagnostic criteria (patients) or scoring over exclusion threshold using the SAPAS screening questionnaire for personality disorders (controls), suggesting that they might show intermediate connectivity patterns, in-between the two groups. The excluded participants were classified at chance level explaining at least part of the lower accuracies in the Referral grouping. This tentatively supports the interpretation that the individuals not matching the criteria for either group exhibited brain connectivity patterns that were particularly difficult to classify as either BPD or control. Thus, it appears particularly important that the current diagnosis and symptoms are carefully evaluated by a clinician rather than relying on old diagnoses or self-reports. However, the low number of excluded participants and other individual differences (e.g. in motion, brain size or education) preclude strong interpretation of the causes that made these individuals particularly difficult to classify.

4.1. Limitations

Importantly, in addition to group differences of interest, there are also other sources of variation in resting state functional connectivity. While the main source of variance seems to be due to individual factors (Gratton et al., 2018), and intrinsic functional connectivity appears largely stable during rest and different audiovisual stimulation conditions (Simony et al., 2016), the test-retest reliability is not perfect and depends on the specific brain regions and the amount of available data (Noble et al., 2017). Moderate individual–task interactions may also exist (Gratton et al., 2018). Reliability might be improved by providing the participants with an attention-inducing naturalistic stimulus, which appears to reduce participants' motion (Vanderwal et al., 2015), at least in children. An engaging stimulus may also reduce the intraindividual variability of connectivity between subsequent measurements, which could arise due to unconstrained, idiosyncratic patterns of thought. Reducing this unwanted variability could potentially even accentuate intergroup variability (for discussion and a conceptual demonstration, see (Finn et al., 2020)). Additional limitations of the study are discussed in the Supplementary Discussion section.

4.2. Conclusions

Our results demonstrate that widespread functional connectivity patterns reliably discriminate between BPD and control participants. However, only a subset of these regions was consistently able to classify patients irrespective of medication as well as group selection and preprocessing strategies suggesting considerable heterogeneity in the patient population. Importantly, the classification results generalized to unbalanced left-out participants. However, the specificity of these findings should be further evaluated in relation to other psychiatric disorders. Low reliability of local link-level differences may explain the lack of consensus in the previous literature. Therefore, it is imperative that the reliability of observations is scrutinized and larger, well-characterized transdiagnostic samples are favored in future studies to avoid discrepant findings and over-interpretation of functional differences associated with psychiatric disorders.

CRediT authorship contribution statement

Juha M. Lahnakoski: Writing – original draft, Visualization, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Tobias Nolte:** Writing – review & editing, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Alec Solway:** Writing – review & editing, Conceptualization. **Iris Vilares:** Writing – review & editing, Conceptualization. **Andreas Hula:** Writing – review & editing, Conceptualization. **Janet Feigenbaum:** Writing – review & editing, Investigation, Conceptualization. **Terry Lohrenz:** Writing – review & editing, Conceptualization. **Brooks King-Casas:** Writing – review & editing, Conceptualization. **Peter Fonagy:** Writing – review & editing, Supervision, Conceptualization. **P. Read Montague:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Leonhard Schilbach:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

All authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.05.125.

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