Transdiagnostic Brain Connectivity Markers of Dissociation during Resting State

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Zhiying Zhao: Took the lead role on conceptualization, methodology, formal analysis and data visualization, as well as writing of the original draft of this manuscript.

Michelle Hampson: was in involved in conceptualization of this manuscript and provided supervision on data analysis and data visualization and writing from early through final drafts.

Tobias Nolte: was research lead and coordinated collection of the self-report, clinical, and imaging dataset, and has curated those data over time. He participated in discussion about the project and edited and contributed content to the manuscript.

Peter Fonagy: discussions about the conceptualization and data collection strategy for this overall dataset. He edited and contributed content to the manuscript.

London Personality and Mood Network: this team of clinicians and research assistants facilitated patient recruitment and aspects of clinical assessments

Brooks King-Casas: was involved in conceptualizing and funding the collection of the overall dataset. Was involved in discussions about conceptualization for this project, and gave edits on the final manuscript.
Terry Lohrenz: was involved in project supervision and administration from data collection through data analysis in this project. He participated in discussion about the project and gave feedback on the manuscript.

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P. Read Montague: conceptualized, directed, and funded the collection of this dataset, was involved in discussions about the conceptualization, analytic strategy, and writing of this manuscript. He read and gave edits on final manuscript.
Key Points

Question Dissociative experiences are common across healthy and psychiatric populations, but it is unclear whether transdiagnostic biomarkers of dissociative traits exist.

Findings We used a data-driven dimensional approach on a large neuroimaging dataset (N=148) with healthy and personality disorder subjects. We identified a significant transdiagnostic association between trait dissociation and global connectivity of the orbitofrontal and inferior temporal cortices.

Meaning The relationship between global brain connectivity and trait dissociation across healthy and patient groups in our data supports the view that dissociation is a transdiagnostic phenomenon with a common neural basis across populations.

Abstract

Importance Dissociation is a clinical phenomenon wherein the normal continuity between aspects of consciousness and experience is disrupted. Pathological dissociative symptoms are present in a number of psychiatric disorders, yet the brain bases of dissociation have primarily been examined within single disorders and findings do not converge across study samples.

Objective To investigate the shared neural underpinnings of dissociation across healthy and clinical populations.

Design This is a cross-sectional study using resting state functional magnetic resonance imaging (fMRI) scans and self-report questionnaires.

Setting Patients with personality disorders were recruited through referrals from mental health services across five London boroughs in the United Kingdom. Healthy controls were also recruited from the London area. Imaging data were collected on Siemens MAGNETOM Trio MRI systems in the Wellcome Trust Centre for Human Neuroimaging at University College London.

Participants A total of 203 participants, including healthy controls as well as individuals with Borderline Personality Disorder (BPD) and Antisocial Personality Disorder (ASPD) were screened using Structured Clinical Interview for DSM-IV Axis II Diagnoses. 148 participants entered the final data analysis after screening for data availability and quality.

Main Outcome(s) and Measure(s) Global connectivity during resting-state fMRI across the whole-brain in healthy and in patients with BPD and ASPD. Trait dissociation as measured by unidimensional Dissociative Experience Scale (DES).

Results Our large dataset (n=148) included 58 healthy controls (mean [SD] age, 27.36 [9.94] years; mean [SD] DES score, 13.48 [11.23]; 23 men [39.7%]), 83 BPD (30.15 [9.70] years; DES score, 32.78 [18.87]; 12 men [14.4%]) and 7 ASPD (27.14 [10.25] years; DES score, 41.84 [25.93]; 7 men [100%]) patients. Our primary analyses identified associations between DES score and centrality in right orbitofrontal and left inferior temporal regions. Exploratory analyses using these two regions as seed-regions further revealed that functional connectivity between the orbitofrontal locus and retrosplenial cortex was negatively related to DES score, while connectivity between the orbitofrontal region and other default mode regions was positively related to DES score.
Conclusions and Relevance These findings converge with previous studies focused on individual populations and suggest that these brain biomarkers represent transdiagnostic markers of dissociation.
Introduction

Dissociation is a clinical phenomenon wherein the normal continuity between aspects of consciousness and experience is disrupted. This can include "disruption of and/or discontinuity in the normal integration of consciousness, memory, identity, emotion, perception, body representation, motor control, and behavior"\(^1\). Dissociation is common across psychiatric disorders, with highest prevalence in people with Dissociative Identity Disorder (DID), Post Traumatic Stress Disorder (PTSD), and Borderline Personality Disorder (BPD)\(^2\).

There are multiple risk factors for dissociation; trauma is one of the best-validated\(^3\). History of childhood abuse increases the likelihood of adult dissociative symptoms, especially longer duration abuse by primary caregivers\(^4\). Alterations in cortical excitatory-inhibitory balance have also been implicated through neuropsychopharmacology in healthy and clinical patients; reduced GABAergic tone combined with serotonergic stimulation provokes dissociative symptoms in the laboratory\(^5\).

Dissociative symptoms can be reliably measured using self-report and interview measures built to capture the transdiagnostic and dimensional nature of dissociation\(^6-8\). For example, many people have had the experience of becoming so absorbed in a book or movie that they didn't hear someone calling from the next room. Fewer people have experienced floating above their own body or finding unfamiliar clothes in their closet. The most commonly used trait dissociation scale, the Dissociative Experience Scale, measures the frequency of a wide range of more and less pathologic dissociative experiences to capture the full range of dissociation along a unidimensional construct\(^8\).

Neuroimaging studies have identified many different candidate brain biomarkers of pathological dissociation by examining differences between highly symptomatic clinical and healthy control subjects\(^9\). In this work, we instead adopted a dimensional approach to identify neural biomarkers that vary continuously with degree of trait dissociation in a large cohort including people with and without psychiatric diagnosis.

Over the past several decades, resting state fMRI has proven a powerful tool for uncovering aberrant intrinsic brain dynamics in mental illnesses\(^10\), and has yielded some successes toward identifying the network bases of dissociation\(^11-13\). Using a whole-brain data-driven approach, the current study sought to investigate how trait dissociation is related to resting state functional connectivity in a large transdiagnostic sample. We used degree centrality (DC), a graph theory based measurement of intrinsic connectivity\(^14\), as the primary outcome measure. We further probed the brain pathways associated with trait dissociation by using the brain structures identified in DC analysis as seed-regions in an exploratory follow-up analysis. In light of evidence for the roles of orbitofrontal cortex (OFC)\(^15-17\) and deep posteromedial cortex function in dissociation\(^18,19\), we expected to see associations between dissociation score and connectivity measures in these two regions. Our cohort of healthy controls and patients with the dissociation-associated disorders (i.e. BPD and antisocial personality disorder (ASPD)) robustly samples participants across a broad range of trait dissociation levels.

Methods

Participants
Participants were drawn from a large research program designed to investigate neuroeconomic behavior in BPD and ASPD compared to healthy participants. Patients with personality disorders were recruited across five London boroughs through referrals by clinicians, (trainee) clinical psychologists, and care coordinators within medical care facilities supported by several London NHS Mental Health Trusts. Healthy control participants were also recruited from the London area. Written informed consent was obtained from the subjects before receiving the assessments using procedures approved by Research Ethics Committee for Wales, 12/WA/0283.

Participants using non-prescribed substances were excluded. Structured Clinical Interview for DSM-IV Axis II Diagnoses (SCID II) was conducted by psychologists to confirm each patient’s referral diagnosis or healthy control status.

From this large study involving several visits and multiple fMRI neuroimaging sessions, we identified 203 participants who completed both self-report scales and a resting state fMRI scan.

**Self-reported dissociative symptoms**

To quantify the extent of dissociative experiences in their daily lives, participants completed the Dissociative Experience Scale (DES) which has shown high validity and reliability in both clinical and non-clinical populations, and has been used to measure dissociation in more than 100 studies. For 28 items, respondents self-report the frequency of each experience from 0-100% of the time. The scale yields an overall score (average of 28 items) and subscale scores for depersonalization, absorption, and amnesia.

**Imaging**

A five-minute resting state scan was performed following an fMRI task run with the order of the task paradigms counterbalanced between participants. Participants were instructed to remain still with eyes open and to let their mind wander. A visual stimulus (Microsoft Windows logo) was presented in the center of the screen, and eye tracking was used to monitor wakefulness. See Supplement for imaging parameters.

**Calculation of global functional connectivity measurements**

After preprocessing, global voxel-wise connectivity was calculated from the resting state scans for the degree centrality of each voxel in the whole brain network (see Supplement for details of preprocessing, centrality calculation, and replication using a different threshold).

**Group-level statistical analyses**

Data-driven multiple regression analyses were performed in SPM12 on the smoothed global connectivity maps to find individual clusters of significant connectivity to dissociation total score.
The model controlled for age, gender, and scanning site. Whole-brain analyses were masked to exclude voxels with > 30% probability of being CSF or skull in the default tissue probability map in SPM12.

In line with recent recommendations on controlling false-discovery rates in fMRI inferences\(^{23}\), a parametric cluster inference method was applied to the t-maps using an initial threshold of \(p < .001\) at peak level (cluster-defining threshold), then correcting for family-wise errors (FWE) at cluster level. Clusters surviving correction were considered significant and were reported with number of voxels and peak coordinates in MNI space.

**Exploratory seed and region-of-interest (ROI) analyses**

To further reveal pair-wise functional connections related to dissociation, we conducted exploratory seed analyses with seed-regions defined by the individual clusters that survived correction in the primary analysis above. Multiple regression analysis was performed on the seed-based functional connectivity maps for each seed-region with DES total score as the covariate of interest. Finally, for both seed and global connectivity analyses, connectivity strength was extracted from each region that survived correction for post-hoc linear regression analysis (details of exploratory analyses in Supplement).

**Results**

**Participants**

After excluding participants missing DES (\(n = 29\)), missing age or gender (\(n = 2\)), or with max head movements > 2 mm or > 2 degrees (\(n = 24\)), 148 participants (58 HC, 83 BPD, 7 ASPD) were included in formal data analyses. Average DES total score in BPD and ASPD here are similar to those in published studies\(^{2,24}\) (Table 1). DES scores differed by group (\(F_{2,145} = 26.047, p < .001, \text{Figure 1}\)), with lower scores in HCs than patients (Cohen \(d = 1.12; 95\% \text{CI}, 0.84-1.55; p < .001\) but no significant difference between patient groups (\(p = .43\)).

**Association between dissociation and global connectivity in the brain**

Across all participants, multiple regression revealed significant positive association (\(p_{\text{FWE}} = .01\)) between DES score and degree centrality of an orbitofrontal cluster extending into anterior cingulate cortex in the right hemisphere (84 voxels; \(x\)-\(y\)-\(z\): 24 33 -12, \(t = 5.28\)) with peak voxel located in Brodmann area (BA) 11 (Figure 2A). DES score also positively correlated with degree centrality of a cluster located in left inferior temporal gyrus (ITG) which partly encompassed BA20 (\(p_{\text{FWE}} = .04, 61\) voxels; \(x\)-\(y\)-\(z\): -54 -33 -30, \(t = 4.59\)) (Figure 2B). In a the same model with correlation threshold of \(r > 0.40\) instead of \(r > 0.25\), both OFC and ITG clusters replicated, and a few new temporal and prefrontal clusters added to the map (\(p_{\text{FWE}} < .05\) in cluster level, Figure S1).

**Exploratory analyses examining brain pathways associated with dissociation and its group differences**
To further explore potential dissociation-related brain pathways involving OFC and ITG, we calculated seed-based functional connectivity maps using the our two identified clusters. First, with the OFC seed-region, functional connectivity between OFC and major default mode network (DMN) nodes other than posterior cingulate cortex (medial prefrontal cortex and bilateral inferior parietal lobules) was positively correlated with DES score. Meanwhile, connectivity between OFC and retrosplenial cortex (RSC) was negatively correlated with DES score. Then, with the left ITG seed-region, interhemispheric connectivity to a fusiform/parahippocampal gyrus cluster positively correlated with DES score (locations in Figure S2, detailed information in Table S1).

For each of the above results, we conducted a post-hoc regression analysis to control for the effect of group on DES score. In this model, all ROIs remained still highly significant predictors of DES score (Table 2), indicating the transdiagnostic nature of these results. Of note, degree centrality in OFC was a significant predictor of DES score within each group, while connectivity between the ITG and left fusiform also had at least trend-level significance within each group (Figure 3). See Table S2 for further details of within-group significant results.

Discussion

To build on previous evidence linking dissociation to alterations in brain activity in specific populations, we employed a transdiagnostic data-driven approach to examine which spontaneous brain connectivity patterns are associated with dissociative traits, independent of clinical status. This approach revealed associations between trait dissociation and global connectivity of OFC and ITG. Exploratory seed analyses further revealed similar relationships between DES score and functional connectivity in pathways connecting OFC to DMN regions as well as an ITG-fusiform pathway.

Our finding in OFC is consistent with evidence from other populations. For example, in a study of PTSD patients, those with dissociative features had a higher mean amplitude of low-frequency fluctuations (mALFF) in OFC than did non-dissociative patients. Using multivariate pattern analysis, the same study also found that mALFF in bilateral OFC played an important role in discrimination of dissociative type PTSD from other PTSD and healthy subjects. OFC has been also implicated in depersonalization disorder (DPD). Depersonalization is a type of dissociative experience characterized by discontinuity in self-awareness. A neurobiological model of DPD has suggested that increased alertness and reduced arousal are related to dysfunctionally heightened top-down control of the insula and limbic structures by the prefrontal cortex. Interestingly, a study comparing neural activity patterns in DPD patients to control populations identified an area of the right ventrolateral prefrontal cortex proximal to the OFC locus in our data that was activated in the DPD patients but not in control subjects in response to aversive stimuli (Figure S3). Two subsequent transcranial magnetic stimulation (rTMS) studies in patients with DPD targeted the same region, and were able to reduce depersonalization symptoms by 27.3% and by 44%. Furthermore, in a different study of DPD patients receiving lamotrigine treatment, another nearby area of ventrolateral prefrontal cortex (Figure S3) was identified as playing a potentially inhibitory role on emotional response. Taken together with our data, these findings highlight the role of right ventrolateral prefrontal cortex in dissociation across clinical populations.

We also found a relationship between dissociative traits and the connectivity between OFC and several DMN nodes, including mPFC and bilateral IPL, and a negative correlation between dissociative traits and
the connection between OFC and the retrosplenial cortex (RSC). Among the major large-scale brain networks, DMN has been most consistently linked to dissociation\textsuperscript{28,29}. A study investigating the brain activity difference between BPD and healthy populations during exposure to painful stimulation reported that expression of the independent component covering RSC during pain exposure was correlated with both borderline symptoms and DES scores\textsuperscript{19}. Furthermore, a segregation between left RSC and the rest of that DMN component was found in the BPD patients. This pattern bears an interesting parallel to our finding that RSC connectivity to OFC had the inverse relationship to dissociation as the other connections between DMN areas and the OFC. One possibility is that the segregation of RSC from the rest of the DMN in patients with dissociation is mediated by these connections with the OFC. Findings from a recent study that functional connectivity between DMN and frontoparietal network is predictive for dissociation severity in women with PTSD similarly suggests an important role of this inter-network connectivity in dissociative experiences\textsuperscript{11}. Using intracranial EEG recordings, the unique role of the RSC in dissociation was highlighted in a recent study that identified an 1-3 Hz rhythmic activity in this region which was associated with the onset of dissociative symptoms during pre-seizure aura in a human patient with epilepsy\textsuperscript{18}. One of the electrodes showing this pattern was precisely homologous to the RSC cluster found in the current study (see Figure S4). Furthermore, brief stimulation of the RSC electrodes replicated the patient’s pre-seizure dissociative experiences\textsuperscript{18}.

Of note, others have linked OFC-limbic connections to trait dissociation and suggested that OFC inhibition of limbic activity may lead to reduced emotional processing\textsuperscript{7}. We did not replicate this link: our findings instead suggest that OFC may play a role in dissociation by disrupting the internal connectivity of the DMN and so altering self-referential processing. These roles for OFC in dissociation may well both be relevant, but the present study (focused on trait, not present-moment dissociation) provides direct support only for the latter. Some of these regions are associated with the DMN; we (Fonagy et al.) have argued elsewhere that the DMN and its role in the mentalizing network could be relevant to the senses of discontinuity and emptiness as they can occur in disorders with prominent dissociative experiences\textsuperscript{30}.

In addition to the OFC locus, our analysis also found an inferior temporal region in which global connectivity was positively related to DES score. ITG activation during exposure to negative facial expressions has been correlated with electrodermal activation in DPD patients\textsuperscript{31}. The correlation between fusiform gyrus connectivity strength and trait dissociation found in the current dataset has been previously observed in a BPD sample\textsuperscript{32}. The implication of the ITG-fusiform pathway in relation to dissociation is a novel finding in the existing body of literature and remains to be replicated and potentially further investigated.

Limitations

The current study has some limitations that future work may address. There is a gender skew in our BPD sample with 85.5% percent of the subjects being women, in line with typically observed clinical trial samples of BPD\textsuperscript{33,34}. Our results are driven primarily by patterns in the BPD and healthy control groups as the ASPD group has a small sample size. The convergence of our findings with those of previous studies in other disorders involving dissociation is encouraging, however, confirmation of these findings in other populations is needed.
Marek et al. (2022) have recently raised concerns about the reproducibility of findings from brain-wide association studies with samples smaller than 1000 participants. Although these concerns clearly merit close attention, our study differs from the Marek et al. work in several ways. The parcellation-based approach used by Marek and colleagues discards a rich source information represented by the pattern of activity within each parcellated region. In contrast, we used a voxel-wise analysis. Also our sample was clinically-enriched rather than dimensional in the general population. Importantly, this study capitalizes on one of the largest BPD neuroimaging datasets reported to date.

Conclusions

The current study found relevant functional connectivity patterns in the orbitofrontal cortex, and exploratory analyses pointed also to connectivity in the retrosplenial cortices and other parts of the DMN that were related to trait dissociation. Importantly, these correlation patterns remained significant when controlling for group membership, and thus represent transdiagnostic brain markers for trait dissociation.

Conflict of Interests

The authors have no conflict of interest to declare.

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References


Figure 1. Boxplot of the DES score in each participant group with the box range from the first to the third quartile. Individual DES scores are denoted with circles, and the median of each group is indicated by the solid lines across the boxes. DES: Dissociative Experience Scale; ASPD: antisocial personality disorder, in red; BPD: borderline personality disorder, in green; HC: healthy controls, in blue.
Figure 2. Dissociation is positively correlated with the degree centrality in orbitofrontal (Panel A) and inferior temporal regions (Panel B). Findings are significant after whole-brain cluster correction.
Figure 3. Linear relationships between DES score and intrinsic network measures of OFC (panel A-E) and ITG (panel F and G) within each subject group. 95% confidence intervals and distributions of the measurements are denoted with colored areas. DES: Dissociative Experience Scale; OFC: orbitofrontal cortex; mPFC: medial prefrontal cortex; IPL: inferior parietal lobule; RSC: retrosplenial cortex; ITG: inferior temporal gyrus; ASPD: antisocial personality disorder; BPD: borderline personality disorder; HC: healthy controls.
Table 1. Demographic information and DES total score of each group

<table>
<thead>
<tr>
<th>Group</th>
<th>Age, mean (SD)</th>
<th>Sex</th>
<th>DES, mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPD</td>
<td>27.143 (10.254)</td>
<td>7/7 males</td>
<td>41.837 (25.925)</td>
</tr>
<tr>
<td>BPD</td>
<td>30.145 (9.697)</td>
<td>12/83 males</td>
<td>32.775 (18.866)</td>
</tr>
<tr>
<td>HC</td>
<td>27.362 (9.941)</td>
<td>23/58 males</td>
<td>13.479 (11.230)</td>
</tr>
</tbody>
</table>

Abbreviations: ASPD = antisocial personality disorder; BPD = borderline personality disorder; HC = healthy controls; SD = standard deviation.

Table 2. Regression analyses controlling for group

<table>
<thead>
<tr>
<th>Network measurement</th>
<th>Coefficient</th>
<th>Std. Error</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree Centrality in OFC</td>
<td>25.405</td>
<td>5.297</td>
<td>4.796</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Degree Centrality in ITG</td>
<td>17.038</td>
<td>4.509</td>
<td>3.778</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>OFC and RSC Connectivity</td>
<td>-69.280</td>
<td>17.533</td>
<td>-3.951</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>OFC and Left IPL Connectivity</td>
<td>49.547</td>
<td>12.970</td>
<td>3.820</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>OFC and Right IPL Connectivity</td>
<td>44.554</td>
<td>13.066</td>
<td>3.410</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>OFC and mPFC Connectivity</td>
<td>38.100</td>
<td>11.870</td>
<td>3.210</td>
<td>.002</td>
</tr>
<tr>
<td>ITG and Fusiform Connectivity</td>
<td>101.167</td>
<td>19.144</td>
<td>5.285</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Note. When controlling for group in separate linear regressions (DES ~ ROI Value + Group), each extracted ROI value significantly predicted DES score. Main effects of group on DES score in these models are not reported.