**Altered brain functional connectome associated with disinhibition across 33 impulsive and compulsive behaviours**

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**Abstract**

Impulsive and compulsive problem behaviours are associated with a variety of mental disorders. Latent phenotyping indicates the expression of impulsive and compulsive problem behaviours is predominantly governed by a transdiagnostic ‘disinhibition’ phenotype. In a cohort of 117 subjects, recruited as part of the Neuroscience in Psychiatry Network (NSPN), we examined how brain functional connectome and network properties relate to disinhibition. Reduced functional connectivity within a subnetwork of frontal (especially right inferior frontal gyrus), occipital, and parietal regions was linked to disinhibition. Findings provide insights into neurobiological pathways underlying the emergence of impulsive and compulsive disorders.

It is increasingly acknowledged that psychiatric symptoms are underpinned by common latent constructs that manifest in an inappropriate or maladaptive manner (1). Specifically, ‘impulsivity’ and ‘compulsivity’ are two such critical constructs that typify a range of disorder presentation, e.g. substance dependence and obsessive-compulsive disorders. Impulsivity encompasses a predisposition towards poorly conceived actions, taking undue risks, and a lack of consideration when making decisions (2). Compulsivity is thought of as an inappropriate and maladaptive persistence of repetitive behaviour, undertaken according to rigid rules and/or as a means of avoiding perceived negative consequences (2). While features of impulsive and/or compulsive behaviour exist in a dimensional fashion within the general population, reflecting a lack of control over thoughts and behaviour, more extreme pathological manifestations underpin a range of psychiatric disorders (2).

Impulsive and compulsive problems are often examined separately as disparate constructs, but the co-occurrence and fluidity by which the two constructs may transition from one to the other suggest some shared variance, and common brain mechanisms, contribute to both (2). Recent work demonstrated that >70% of symptom expression across 33 impulsive and compulsive behaviours (as measured by the Impulsive-Compulsive Behaviours Checklist (ICBC)) could be statistically accounted for by a trans-diagnostic ‘disinhibition’ phenotype (3). Conceptually, disinhibition reflects a lack of top-down executive control, reflected in both cognitive inflexibility-driven compulsivity as well as impulsivity (2). Yet while a wealth of evidence documents brain network reorganization across a range of impulsivity/compulsivity related mental disorders, as compared to controls, little is known about network characteristics associated with disinhibition as viewed dimensionally along a continuum.

Brain network dysregulation has been demonstrated to cut across diagnostic boundaries of psychiatric disorders, representing individual variability (e.g. impulsivity and compulsivity) that guide motivated behaviour. In this vein, deciphering the link between brain network topology and latent behavioural phenotypes (such as disinhibition) can be considered vital to clarifying the neurobiology of impulsive and compulsive disorders (2). The primary aim of this study was to use connectomics and graph theory to identify dysregulated brain networks associated with disinhibition, and therefore implicated as common substrate across impulsive and compulsive behaviors.

**Method**

Participants were recruited from a larger cohort of adolescents and young adults from the NSPN (Neuroscience in Psychiatry Network) study (4). A detailed description of the recruitment methods and sample are provided in (4). In brief, NSPN was set up as a demographically representative sample of the UK population using a stratified recruitment design. Participants were entered on the basis of having no history of psychiatric treatment or neurological disorder, head injury or learning disability. Measures of impulsivity and compulsivity symptoms were collected with the ICBC, 3 years after enrolment. The ICBC assesses for the frequency of 33 common impulsive and compulsive problem behaviours, including: washing, smoking, gambling etc. (3,5). In a previous paper, confirmatory factor analysis on 654 participants’ ICBC response identified a single latent factor (termed ‘disinhibition’) accounting for ~70% of the variance in participants’ ICBC scores (3). See Supplementary Table 1 for ICBC checklist items and loadings.

***MRI acquisition and preprocessing***

From the original NSPN cohort, a random subset of participants completed neuroimaging, of whom data were available from 117 who had also undertaken the subsequent round collecting the ICBC data. The study was approved by Research Ethics Committee and individuals provided informed consent.

Brain scans were conducted at 3 sites, two at the University of Cambridge (the Wolfson Brain Imaging Centre; the Medical Research Council Cognition & Brain Sciences Unit) and one at University College London (the Welcome Trust Functional Imaging Laboratory), all with identical 3T, 32-channel MRI systems (Magnetom TIM Trio) and a unified acquisition sequence. Resting-state functional scans were obtained with a multi-echo echoplanar imaging (ME-EPI) sequence. Scanner detail and preprocessing steps can be found in (6), but briefly, multi-echo ICA (ME-ICA) was used to preprocess acquired datasets and remove noise and other sources of variance. The retained BOLD contrast was wavelet bandpass filtered (0.025-0.111 Hz). Mean framewise displacement (FD) across time series were determined for each participant, and participants with high in-scanner motion (µ(FD) > 0.3mm or max(FD) > 1.3mm) were excluded.

***Parcellation and network-based statistics (NBS) analysis***

Functional MRI images were parcellated by subdividing the Desikan-Kiliany anatomical atlas into 308 cortical parcels of approximately equal surface area (~500mm2) and 16 subcortical regions. BOLD time series were estimated from the average over all voxels within each of the 324 parcels (nodes). Pearson correlation was calculated between the timeseries of each pair of nodes to determine their functional connectivity strength, resulting in a symmetric 324x324 connectivity matrix for each participant (Figure 1). The resultant matrices were Fisher’s r-to-z transformed to improve normality of the correlation estimates.

The NBS connectome software package (version 1.2, <https://www.nitrc.org/projects/nbs/>) was used to assess for association between interregional connectivity matrix and disinhibition scores, controlling for age, gender, and IQ. IQ was recorded using the Wechsler Abbreviated Scale of Intelligence (WASI-II). This first included mass univariate testing at each edge, with a primary component-forming threshold of p<.0001 uncorrected. Each identified component (i.e. topologically connected subnetwork) was then assessed at (10,000 permutations) using a family-wise error rate (FWER)-corrected level of p<0.05.

***Graph theory analysis***

Graph theoretic analyses (i.e. modelling the brain network as a graph of interconnected regions/nodes) is further used to examine specific brain connection properties. The Brain Connectivity Toolbox (7) is used, and properties that are examined include - local network properties (i.e. (i) nodal degree, (ii) normalized betweenness centrality, (iii) local efficiency, and (iv) clustering coefficient) and global network properties (i.e. (i) global efficiency and (ii) transitivity). These properties were examined across sparsity thresholds of 0.05 to 0.2 (at increments of 0.01). The areas under the curve across the threshold range for the listed properties were computed, and partial correlation was used to determine if any of these network properties were significantly associated with disinhibition, again controlling for age, gender, and IQ. Local and global properties were assessed at p<.000154 and p<.025 respectively (i.e. Bonferroni corrected for number of nodes and number of global properties respectively.

**Results**

The 117 participants (71 female) had a mean age of 22.6 (SD=2.7, range=18-28) years, and mean IQ of 112.5 (SD=10.7). Disinhibition factor score estimates ranged from -1.38 to 2.28 (mean=0.05, SD=0.81). NBS analysis revealed a subnetwork consisting of 15 edges across 15 regions, that was significantly negatively associated with disinhibition scores (FWER-corrected p=.0203). The connections primarily linked the right inferior frontal brain region (i.e. right pars opercularis) to bilateral lateral occipital regions (9 out of 15 connections/edges), and the right lateral occipital region to the right parietal (i.e. supramarginal) region (4 edges). Two other edges connect the right pars opercularis to the left precentral and left superior frontal gyri respectively. See Figure 1 for brain networks, visualized using the BrainNet Viewer (8). Examination of local (all *p*>.00039, r<0.32) and global (all *p*>.016, r<0.23) network metrics revealed no other significant association between network measures and disinhibition scores, at the Bonferroni correction threshold.

[Figure 1]

**Discussion**

This study demonstrates connectome-level variation in brain functional networks associated with disinhibition, providing first evidence of common functional substrates contributing to both impulsive and compulsive behaviour problems. Reduced network connections across a subnetwork of frontal (specifically right inferior frontal), parietal, and occipital regions were observed in association with increased disinhibition. Over half of the affected edges connect the bilateral occipital regions to the right inferior frontal region – specifically, the pars opercularis. These changes were regionally specific and did not reflect changes in global network properties. These data indicate that variation in connectivity is related to disinhibition, which was driven primarily by connection to the inferior frontal region (as measured by total number of connecting edges). This converges with other studies emphasizing the central role of the inferior frontal brain region in response inhibition and maladaptive behavioral problems (2). The inferior frontal and occipital cortices are co-activated and show marked functional coupling when inhibitory control is required (9). Additionally, reduced inhibition-related functional connectivity between frontal and posterior brain regions constitutes a candidate vulnerability marker for OCD (10). The current data suggest that aberrant long-distance resting state connections along the anterio-posterior axis may play a role in predisposing towards disinhibited behaviour.

**Limitations and Conclusion**

The original NSPN cohort was recruited to be epidemiologically representative of the general UK population. This reduces selection biases inherent in clinical samples but may limit the applicability of findings to those with more severe psychopathology (i.e. higher disinhibition). Another limitation is that the study shows association not causality. Future work should examine what precise underlying mechanisms (psychological and biological) contribute to the observed link between disinhibition and brain dysconnectivity. Yet findings provide insights into neurobiological processes that confer vulnerability to many types of problematic impulsive and compulsive behaviours, and therefore may be relevant to the search for trans-diagnostic heuristics. Extending these techniques into patient populations, and larger imaging cohorts, will ideally refine our current understanding of the etiology and course of psychiatric disorders and the role of common latent phenotypes in the emergence of psychiatric conditions. This will require the inclusion of appropriate measurement tools for impulsivity and compulsivity in large-scale population studies, which have typically overlooked such dimensional measures in favour of binary measures or interrogation of single disorder symptomatology (e.g. OCD).

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**Author Contributions**

R.R-G., R.B., R.H., I.G., P.B.J., R.D., E.T.B., J.E.G., M.Y., and S.R.C. were responsible for study conceptualization and data collection. Y.C., M.Y., and S.R.C. formulated the specific research question and contributed to the interpretation of data. Y.C., C.S., R.R-G., and J.T. conducted the analysis. Y.C. drafted the paper with support and input from all authors.

**Data Availability**

The data that support the findings of this study are available from the corresponding author, Y.C., upon reasonable request.

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**Figure Caption**

**Figure 1.** (a) Average fMRI correlation matrix. (b) Subnetwork showing reduced functional connectivity associated with latent disinhibition phenotype, assessed using the network-based statistics (NBS) software package and visualized using the BrainNet Viewer. (b) The subnetwork consists of 15 edges across 15 regions, connecting (1) the right pars opercularis (in deep blue) to bilateral lateral occipital regions (in red and light blue), (2) the right lateral occipital region to the right supramarginal region (in pink), as well as the right pars opercularis to (3) the left precentral (in yellow) and (4) left superior frontal gyri (green) respectively. lLOc = left lateral occipital; rLOc = right lateral occipital; lPrg = left precentral gyrus; rPOp = right pars opercularis; lSFg = left superior frontal gyrus; rSMg = right supramarginal.