A Connectome Wide Functional Signature of Broad Risk for Mental Illness

Maxwell L. Elliott[1], Adrienne Romer[1], Annchen R. Knodt[1] and Ahmad R. Hariri[1]

[1]Laboratory of NeuroGenetics, Department of Psychology & Neuroscience, Duke University, Durham, NC, USA

Abstract

High rates of comorbidity, shared risk, and overlapping therapeutic mechanisms have led psychopathology research towards transdiagnostic dimensional investigations of clustered symptoms. One influential framework accounts for these transdiagnostic phenomena through a single general factor, sometimes referred to as the 'p' factor, associated with risk for all common forms of mental illness. Here we build on past research identifying unique structural neural correlates of the p factor by conducting a data-driven analysis of connectome wide intrinsic functional connectivity. We demonstrate that higher p factor scores and associated risk for common mental illness maps onto hyper-connectivity between visual association cortex and both frontoparietal and default mode networks. These results provide initial evidence that the broad risk for common forms of mental illness is associated with patterns of inefficient connectome wide intrinsic connectivity supporting executive control and self-referential processes, which are often impaired across categorical disorders.

Emerging research has identified a general factor of psychopathology that accounts for shared risk among internalizing, externalizing, and thought disorders across diverse samples[1,2]. Moreover, this general psychopathology or 'p' factor[3] provides a framework for explaining the high rates of comorbidity as well as the shared genetic variance among categorical mental disorders[4,5]. As such, the p factor represents a potentially useful avenue for better understanding the shared and unique etiology of common mental illness. However, the biological mechanisms through which the p factor confers general risk for psychopathology remain unclear. Identifying such mechanisms is necessary for effectively leveraging the p factor to derive novel targets for clinical intervention and prevention.

Clinical neuroscience has begun to adapt transdiagnostic methodologies to accelerate the search for common neurobiological abnormalities across disorders[6]. For example, a recent large meta-analysis of six categorical disorders reported a shared pattern of reduced gray matter volume in a distributed network supporting attention and cognitive control[7]. In addition, we have recently examined the structural neural correlates of the p factor specifically[8]. In our work, higher p factor scores and thus risk for common mental illness was associated with reduced gray matter volumes in the occipital lobes and neocerebellum. Furthermore, higher p factor scores were associated with reduced fractional anisotropy in pontine pathways linking the neocerebellum with the thalamus and prefrontal cortex. Our observed patterns along with those of the recent meta-analysis suggest that higher p factor scores contribute to broad risk for common forms of mental illness through alterations in networks critical for feed-forward monitoring of information processing and executive control. However, the putative functional consequences of these observed structural associations have not yet been examined.

Resting-state functional connectivity has emerged as a powerful tool in clinical neuroscience because it can be readily administered across patient populations[9,10], demonstrates trait-like stability[11] as well as moderate heritability[12,13], and represents a powerful probe of the intrinsic architecture of neural networks that play a primary role in shaping task-based network activity and associated behaviors[14]. In addition, altered intrinsic functional connectivity within the default mode network (DMN), and frontoparietal network (FPN), both of which are linked to higher order cognition, have been broadly linked to psychopathology across categorical disorders[15–17]. Thus, resting-state measures of intrinsic network connectivity represent one avenue for extending the structural associations of the p factor to variability in functional neural dynamics representing mechanisms through which risk may emerge.

Here, we investigate intrinsic functional connectivity correlates of the p factor in a volunteer sample of 614 university students from the Duke Neurogenetics Study. While our previous research in this sample identified discrete structural correlates of the p factor in the occipital lobes, neocerebellum, and pons, we opted for a whole-brain exploratory analysis of intrinsic connectivity to better capture possible functional differences beyond these regions and impose minimal assumptions about the nature of p factor associations in the brain. Thus, we performed a Connectome-Wide Association Study (CWAS)[18] of the p factor, a data driven method for identifying resting-state seeds whose whole brain connectivity are associated with the p factor in the absence of *a priori* assumptions about brain regions or networks.

Results

Demographics. From the 614 participants who completed two resting-state scans, 605 had data that survived quality control procedures. Of these, 336 were women, and the mean age was

20.23±1.19 years old. Scores for the p factor ranged from 76.71to 191.96 with a mean of 99.80, sd of 15.39.

Multi-dimensional matrix regression. Of the 1015 ROIs investigated, multi-dimensional matrix regression (MDMR) analysis revealed four regions with whole-brain connectivity patterns significantly associated with p factor scores: left lingual gyrus, right middle occipital gyrus, and two adjacent parcels of the left middle occipital gyrus (figure 1).

Follow-up intrinsic connectivity analyses. The follow-up connectivity analyses of each seed identified through MDMR revealed the primary network associations for each seed as well as their pattern of whole-brain connectivity associated with p factor scores. These analyses showed striking convergence across MDMR selected ROIs wherein the mean whole-brain pattern of connectivity for each seed showed subtle variation, but largely outlined the canonical resting-state visual processing network[19]. The connectivity of each ROI with visual and somatosensory regions decreased with increasing p factor scores, while the connectivity between each ROI and transmodal association regions[20] increased with increasing p scores (figure 2).

Further analyses were conducted to better characterize the above consistent patterns of p factor associations with the intrinsic connectivity of all seeds by averaging the independent whole-brain connectivity maps. The resulting average z-scores were summarized for each of the 7 Yeo networks[21] to quantify their respective contribution to the associations with p factor scores (figure 3). These analyses revealed the DMN and FPN as the major networks for which intrinsic functional connectivity was positively correlated with p factor scores. In contrast, a more modest

but notable negative correlation was observed between p factor scores and the intrinsic functional connectivity between the visual association cortex and somatomotor network.

Discussion

Here, we provide a novel extension of prior structural neural correlates of the p factor to the intrinsic architecture of the whole-brain functional connectome. Our unconstrained connectome wide MDMR analysis revealed a circumscribed relationship between p factor scores and the whole-brain intrinsic connectivity of nodes in visual association cortex, which is consistent with our earlier work finding a negative correlation between p factor scores and gray matter volume in the occipital cortex[8]. Further investigation of the patterns of intrinsic connectivity driving this relationship primarily implicated hyper-connectivity between visual association cortex and heteromodal frontoparietal and default mode networks. While the visual association cortex and the heteromodal default mode and frontoparietal networks represent opposite ends of the sensory processing hierarchy,[20] their dynamic interactions have been shown to be an important component of successful goal-directed behavior[22–24].

The frontoparietal network in particular has been linked to the core cognitive faculty of executive control,[14,25,26] which contributes to mental health and general well-being by shaping successful goal directed behavior[27]. Fittingly, disrupted FPN activity has been linked to psychopathology across categorical disorders including schizophrenia[28], depression,[29] and bipolar disorder[30]. Building off of this body of research, an emerging theory suggests that the relative integrity of the FPN and associated executive control mechanisms are fundamental for the capacity to self-regulate, manage symptoms, and succeed in treatment across disorders.[15]. Our current findings are consistent with this framework by demonstrating that higher p factor scores regardless

of diagnosis are associated with relative hyper-connectivity of the FPN with the visual association cortex.

Regulation and suppression of incoming sensory information is an important component of goal directed behavior and has been linked to functional connectivity between the FPN and visual association cortex[31,32]. Although speculative, our finding may indicate more effortful or less efficient integration of bottom-up sensory information with attentional demands and executive control processes in those at higher risk for mental illness. This pattern is further consistent with our earlier structural analyses linking higher p factor scores with lower structural integrity of cerebello-thalamo-cerebro-cortical circuits supporting feed-forward executive control and monitoring of goal-directed behaviors[8].

In addition to the frontoparietal network, our analyses implicate hyper-connectivity between the visual association cortex and default mode network as a function of higher p factor scores. The default mode network has been generally linked to introspective thought, autobiographical memory, and future oriented thought[33]. Interestingly, DMN activity is suppressed in attention demanding tasks[33,34] and altered DMN activity has been broadly observed across categorical psychiatric disorders[16,35]. Visual association cortex connectivity with the DMN has been suggested to be important in the suppression of internally generated distracting information[31]. Against this background, our observed association between higher p factor scores and hyper-connectivity between the DMN and visual association cortex suggests that broad risk for mental illness may be related to more effortful or less efficient regulation of internally generated thoughts and information that could have functional consequences in the context of competing attentional demands between internal generated thought and incoming sensory information.

While providing initial evidence that broad risk for all forms of common mental illness is manifest as alterations in the intrinsic connectivity of functional neural networks, our analyses were exploratory by design and replication is needed. Given prior research implicating the frontoparietal and default mode networks across categorical disorders, we focused our above discussion on the potential relevance of intrinsic connectivity between visual association cortex and these networks in the emergence of broad risk for mental illness. While the intrinsic connectivity of these networks also exhibited an outsized influence on the association with p factor scores, variation between visual association cortex and other resting-state networks contributed as well, albeit more modestly (figure 3). MDMR uses information from all whole-brain connections in selecting seeds, and the inferential significance comes from the aggregate of connections rather than any one in particular. Thus, formally testing the relative contributions of different networks is not typically conducted. While we think future studies of the p factor will benefit from using our observations of intrinsic connectivity between visual association cortex and both DMN and FPN as an a priori starting point, the potential relevance of other networks should not be ignored until the patterns reported herein are replicated.

Additional limitations, which can be addressed in future research, include the relatively limited range of psychopathology, especially severe forms including psychosis, represented in our volunteer sample of young adults. Future research should extend our analyses to more diverse populations including individuals with severe mental illness. Our current analyses were also limited to the intrinsic connectivity of nodes within the cerebrum as our resting-state fMRI acquisition protocol did not afford full coverage of the cerebellum, including the neocerebellar subregion identified in our earlier structural analyses. Thus, we are unable to determine the relationship between p factor scores and the intrinsic functional connectivity of the cerebellum.

We anticipate that current state-of-the-art multiband image acquisition protocols will routinely allow for full coverage of the cerebellum and, subsequently, direct analyses of how its intrinsic connectivity scales as a function of p factor scores. The observational nature of our study represents another limitation as we cannot establish causal links between p factor scores and intrinsic connectivity. Longitudinal designs may better address causality and temporal order of these phenomena. Future research employing transcranial magnetic stimulation, closed-loop fMRI, and intervention designs can further map causal relationships.

These limitations notwithstanding, our current work provides initial evidence for unique connectome wide functional signatures of the p factor. Consistent with emerging transdiagnostic and dimensional research into the neural basis of psychopathology[7,8,36], our analyses reveal that increased broad risk for all common forms of mental illness is associated with higher intrinsic connectivity between visual association cortex and both frontoparietal and default mode networks. Such hyper-connectivity suggests that increased risk for psychopathology may be manifest as greater effortful or less efficient executive control as well as poor regulation of self-referential information processing. These patterns place alterations of the functional connectome squarely in the middle of converging theories of network dysfunction in psychopathology, further suggesting the p factor as a promising tool in clinical neuroscience.

Online Methods

Participants. Data were available from 614 university students who successfully completed the Duke Neurogenetics Study (DNS). All participants provided informed consent in accordance with the Duke University Medical Center Institutional Review Board guidelines before participation. All participants were in good general health and free of the following study conditions: (1) medical

diagnoses of cancer, stroke, head injury with loss of consciousness, untreated migraine headaches, diabetes requiring insulin treatment, chronic kidney or liver disease; (2) use of psychotropic, glucocorticoid or hypolipidemic medication; and (3) conditions affecting cerebral blood flow and metabolism (e.g., hypertension).

Clinical Diagnosis. Current and lifetime DSM-IV Axis I disorder or select Axis II disorders (antisocial personality disorder and borderline personality disorder), was assessed with the electronic Mini International Neuropsychiatric Interview[37] and Structured Clinical Interview for the DSM-IV subtests[38] respectively. Importantly, neither current nor lifetime diagnosis were exclusion criterion, as the DNS seeks to establish broad variability in multiple behavioral phenotypes related to psychopathology. Allowing for a broad spectrum of symptoms is particularly critical for accurately deriving p factor scores. Nevertheless, no participants, regardless of diagnosis, were taking any psychoactive medication during or at least 14 days prior to their participation. Of the 605 participants with data included in our analyses, 133 individuals had at least one DSM-IV diagnosis, including 76 with alcohol use disorders, 24 with non-alcohol substance use disorders, 33 with major depression disorder, 26 with bipolar disorder, 7 with panic disorder (no agoraphobia), 9 with panic disorder including agoraphobia, 4 with social anxiety disorder, 8 with generalized anxiety disorder, 10 with obsessive compulsive disorder, and 7 with eating disorders.

Derivation of p factor scores. In previous work[8], our group replicated the p factor in the DNS using confirmatory factor analysis of self-report and diagnostic interview measures of internalizing, externalizing, and thought disorder symptoms. These p factor scores were extracted

using the standard regression method from those analyses, and standardized to a mean of 100 (SD = 15), with higher scores indicating a greater propensity to experience all forms of psychiatric symptoms. The current analyses were conducted in a subsample of 614 subjects of the original 1246 participants for whom there was resting-state fMRI data.

Image acquisition. Each participant was scanned using one of two identical research-dedicated GE MR750 3 T scanners equipped with high-power high-duty-cycle 50-mT/m gradients at 200 T/m/s slew rate, and an eight-channel head coil for parallel imaging at high bandwidth up to 1MHz at the Duke-UNC Brain Imaging and Analysis Center. A semi-automated high-order shimming program was used to ensure global field homogeneity. A series of 34 interleaved axial functional slices aligned with the anterior commissure-posterior commissure plane were acquired for full-brain coverage using an inverse-spiral pulse sequence to reduce susceptibility artifacts (TR/TE/flip angle=2000 ms/30 ms/60; FOV=240mm; 3.75×3.75×4mm voxels; interslice skip=0). Four initial radiofrequency excitations were performed (and discarded) to achieve steady-state equilibrium. For each participant, 2 back-to-back 4-minute 16-second resting state functional MRI scans were acquired. Participants were instructed to remain awake, with their eyes open during each resting state scan. To allow for spatial registration of each participant's data T1-weighted images were obtained using a 3D Ax FSPGR BRAVO with the following parameters: TR = 8.148 ms; TE = 3.22 ms; 162 axial slices; flip angle, 12°; FOV, 240 mm; matrix =256×256; slice thickness = 1 mm with no gap; and total scan time = 4 min and 13 s.

Image Processing. Anatomical images for each subject were skull-stripped, intensity-normalized, and nonlinearly warped to a study-specific average template in the standard stereotactic space of

the Montreal Neurological Institute template using the ANTs SyN registration algorithm[39,40]. Time series images for each subject were despiked, slice-time-corrected, realigned to the first volume in the time series to correct for head motion using AFNI tools[41], coregistered to the anatomical image using FSL's Boundary Based Registration[42], spatially normalized into MNI space using the non-linear ANTs SyN warp from the anatomical image, resampled to 2mm isotropic voxels, and smoothed to minimize noise and residual difference in gyral anatomy with a Gaussian filter set at 6-mm full-width at half-maximum. All transformations were concatenated so that a single interpolation was performed.

Time-series images for each participant were furthered processed to limit the influence of motion and other artifacts. Voxel-wise signal intensities were scaled to yield a time series mean of 100 for each voxel. Motion regressors were created using each subject's 6 motion correction parameters (3 rotation and 3 translation) and their first derivatives[43,44] yielding 12 motion regressors. White matter (WM) and cerebrospinal fluid (CSF) nuisance regressors were created using CompCorr[45]. Images were bandpass filtered to retain frequencies between .008 and .1 Hz, and volumes exceeding 0.25mm frame-wise displacement or 1.55 standardized DVARS[46,47] were censored. Nuisance regression, bandpass filtering and censoring for each time series was performed in a single processing step using AFNI's 3dTproject. Participants were excluded if they had less than 185 TRs left after censoring (resulting in inadequate degrees of freedom to perform nuisance regressions), resulting in a final sample of 605 subjects.

CWAS. To make the analysis computationally tractable, time-series were extracted from a parcellated atlas instead of using voxelwise data. We used the Lausanne atlas parcellated into 1015 equally sized regions through the program easy_lausanne

(github.com/mattcieslak/easy_lausanne). Time-series data for each subject were then processed using CWAS. Described extensively elsewhere[18], CWAS consists of 3 processing steps. First, beginning with a single ROI time-series, seed-based connectivity analysis is conducted to generate a whole-brain functional connectivity map for each participant. Second, the average distance (1 minus the Pearson correlation) between each pair of participant's functional connectivity maps is computed, resulting in a distance matrix encoding the multivariate similarity between each participant's connectivity map. Finally, multi-dimensional matrix regression (MDMR) is used to generate a pseudo-F statistic quantifying the strength of the association between the phenotype of interest, here p factor scores, and the distance matrix created in the second step. The advantage of MDMR is allowing covariates to be entered into the regression and utilizing non-parametric permutation to generate p-values for each ROI. These three steps are repeated for each of the 1015 ROIs, resulting in a whole-brain map that represents the association between p factor scores and whole-brain connectivity at each ROI. CWAS was performed to identify seed regions with whole-brain patterns of connectivity are related to p factor scores. Participant sex was included as a covariate, and 500,000 permutations were performed to generate p-values. To minimize false positives across the 1,015 ROIs, a false discovery rate[48] (FDR) correction was applied.

Seed-based analyses. MDMR identifies a set of ROIs with patterns of whole-brain connectivity associated with p factor scores. However, it is still unclear how the connectivity of these ROIs relates to the scores. Previous research using CWAS[18,36,49] has demonstrated the utility of using traditional seed-based connectivity follow-up analyses to better understand the networks and brain regions that drive the associations discovered through MDMR. Similar analyses were performed here for each ROI identified via MDMR. Seed-based connectivity maps were created and

correlations were converted to Z statistics via the Fischer R to Z transform. Whole-brain correlations between these connectivity values and p factor scores were calculated, including sex as a covariate. Importantly, these follow-up analyses do not represent independent statistical tests as they were performed posthoc to the family wise error controlled MDMR findings. Accordingly, these followup analyses maps are not thresholded to visualize all information that was relevant to the MDMR step.

Acknowledgements and Disclosures

We thank the Duke Neurogenetics Study participants and the staff of the Laboratory of NeuroGenetics. The Duke Neurogenetics Study received support from Duke University as well as US-National Institutes of Health grants R01DA033369 and R01DA031579. ARK, and ARH received further support from US-National Institutes of Health grant R01AG049789. MLE was supported by the National Science Foundation Graduate Research Fellowship under Grant No. NSF DGE-1644868. The authors declare no competing financial interests.

References

1. Lahey BB, Applegate B, Hakes JK, Zald DH, Hariri AR, Rathouz PJ. Is there a general factor of prevalent psychopathology during adulthood? *J Abnorm Psychol*. 2012;121(4):971-977. doi:10.1037/a0028355.
2. Lahey BB, Krueger RF, Rathouz PJ, Waldman ID, Zald DH. A hierarchical causal taxonomy of psychopathology across the life span. *Psychol Bull*. 2017;143(2):142-186. doi:10.1037/bul0000069.
3. Caspi A, Houts RM, Belsky DW, et al. The p factor: One general psychopathology factor in the structure of psychiatric disorders? *Clin Psychol Sci*. 2014;2(2):119-137. doi:10.1177/2167702613497473.
4. Clark LA, Watson D, Reynolds. Diagnosis and classification of psychopathology: Challenges to the current system and future dire. *Annu Rev Psychol*. 1995;46. https://media-proquest-com.laneproxy.stanford.edu/media/pq/classic/doc/8748368/fmt/pi/rep/NONE?cit%3Aauth=Clark%2C+L+A%3BWatson%2C+D%3BReynolds%2C+S&cit%3Atitle=Diagnosis+and+classification+of+psychopathology%3A+Challenges+to+the+current+system+and+future.
5. Lee SH, Ripke S, Neale BM, et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet*. 2013;45(9):984-994. doi:10.1038/ng.2711.
6. Zald DH, Lahey BB. Implications of the Hierarchical Structure of Psychopathology for Psychiatric Neuroimaging. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2017. doi:10.1016/j.bpsc.2017.02.003.
7. Goodkind M, Eickhoff SB, Oathes DJ, et al. Identification of a Common Neurobiological Substrate for Mental Illness. *JAMA Psychiatry*. 2015;72(4):305. doi:10.1001/jamapsychiatry.2014.2206.
8. Romer AL, Knodt AR, Houts R, et al. Structural alterations within cerebellar circuitry are associated with general liability for common mental disorders. *Mol Psychiatry*. 2017;(February):1-7. doi:10.1038/mp.2017.57.
9. Greicius M. Resting-state functional connectivity in neuropsychiatric disorders. *Curr Opin Neurol*. 2008;21(4):424-430. doi:10.1097/WCO.0b013e328306f2c5.
10. Fox MD. Clinical applications of resting state functional connectivity. *Front Syst Neurosci*. 2010;4(June). doi:10.3389/fnsys.2010.00019.
11. Shehzad Z, Kelly AMC, Reiss PT, et al. The resting brain: Unconstrained yet reliable. *Cereb Cortex*. 2009;19(10):2209-2229. doi:10.1093/cercor/bhn256.
12. Glahn DC, Winkler AM, Kochunov P, et al. Genetic control over the resting brain. *Proc Natl Acad Sci U S A*. 2010;107(3):1223-1228. doi:10.1073/pnas.0909969107.
13. Ge T, Holmes AJ, Buckner RL, Smoller JW, Sabuncu MR. Heritability analysis with repeat measurements and its application to resting-state functional connectivity. *Proc Natl Acad Sci*. 2017;114(21):5521-5526. doi:10.1073/pnas.1700765114.
14. Cole MW, Reynolds JR, Power JD, Repovs G, Anticevic A, Braver TS. Multi-task connectivity reveals flexible hubs for adaptive task control. *Nat Neurosci*. 2013;16(9):1348-1355. doi:10.1038/nn.3470.
15. Cole MW, Repovš G, Anticevic A. The Frontoparietal Control System. *Neurosci*. 2014;20(6):652-664. doi:10.1177/1073858414525995.
16. Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJS. Default-mode brain dysfunction in mental disorders: A systematic review. *Neurosci Biobehav Rev*.

2009;33(3):279-296. doi:10.1016/j.neubiorev.2008.09.002.
17. Buckholtz JW, Meyer-Lindenberg A. Psychopathology and the Human Connectome: Toward a Transdiagnostic Model of Risk For Mental Illness. *Neuron*. 2012;74(6):990-1004. doi:10.1016/j.neuron.2012.06.002.
18. Shehzad Z, Kelly C, Reiss PT, et al. A multivariate distance-based analytic framework for connectome-wide association studies. *Neuroimage*. 2014;93(P1):74-94. doi:10.1016/j.neuroimage.2014.02.024.
19. Calhoun VD, Adali T, McGinty VB, Pekar JJ, Watson TD, Pearlson GD. fMRI activation in a visual-perception task: network of areas detected using the general linear model and independent components analysis. *Neuroimage*. 2001;14(5):1080-1088. doi:10.1006/nimg.2001.0921.
20. Margulies DS, Ghosh SS, Goulas A, et al. Situating the default-mode network along a principal gradient of macroscale cortical organization. *Proc Natl Acad Sci U S A*. 2016;113(44):12574-12579. doi:10.1073/pnas.1608282113.
21. Yeo BTT, Krienen FM, Sepulcre J, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol*. 2011;106:1125-1165. doi:10.1152/jn.00338.2011.
22. Chadick JZ, Zanto TP, Gazzaley A. Structural and functional differences in medial prefrontal cortex underlie distractibility and suppression deficits in ageing. *Nat Commun*. 2014;5(May):4223. doi:10.1038/ncomms5223.
23. Gazzaley A, Rissman J, Cooney J, et al. Functional interactions between prefrontal and visual association cortex contribute to top-down modulation of visual processing. *Cereb Cortex*. 2007;17(SUPPL. 1):125-135. doi:10.1093/cercor/bhm113.
24. Gazzaley A, Nobre AC. Top-down modulation: Bridging selective attention and working memory. *Trends Cogn Sci*. 2012;16(2):129-135. doi:10.1016/j.tics.2011.11.014.
25. Ptak R. The Frontoparietal Attention Network of the Human Brain: Action, Saliency, and a Priority Map of the Environment. *Neurosci*. 2012;18(5):502-515. doi:10.1177/1073858411409051.
26. Zanto TP, Gazzaley A. Fronto-parietal network: Flexible hub of cognitive control. *Trends Cogn Sci*. 2013;17(12):602-603. doi:10.1016/j.tics.2013.10.001.
27. Diamond A. Executive Functions. *Annu Rev Psychol*. 2013;64(1):135-168. doi:10.1146/annurev-psych-113011-143750.
28. Barch DM, Ceaser A. Cognition in schizophrenia: Core psychological and neural mechanisms. *Trends Cogn Sci*. 2012;16(1):27-34. doi:10.1016/j.tics.2011.11.015.
29. Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA. Large-Scale Network Dysfunction in Major Depressive Disorder A Meta-analysis of Resting-State Functional Connectivity. *JAMA psychiatry*. 2015;72(6):603-611. doi:10.1001/jamapsychiatry.2015.0071.
30. Anticevic A, Cole MW, Repovs G, et al. Characterizing thalamo-cortical disturbances in Schizophrenia and bipolar illness. *Cereb Cortex*. 2014;24(12):3116-3130. doi:10.1093/cercor/bht165.
31. Chadick JZ, Gazzaley A. Differential coupling of visual cortex with default or frontal-parietal network based on goals. *Nat Neurosci*. 2011;14(7):830-832. doi:10.1038/nn.2823.
32. Karten A, Pantazatos SP, Khalil D, Zhang X, Hirsch J. Dynamic coupling between the lateral occipital-cortex, default-mode, and frontoparietal networks during bistable perception. *Brain Connect*. 2013;3(3):286-293. doi:10.1089/brain.2012.0119.

33. Raichle ME. The Brain's Default Mode Network. *Annu Rev Neurosci*. 2015;38(1):433-447. doi:10.1146/annurev-neuro-071013-014030.
34. Buckner RL, Andrews-Hanna JR, Schacter DL. The Brain's Default Network. *Ann N Y Acad Sci*. 2008;1124(1):1-38. doi:10.1196/annals.1440.011.
35. Whitfield-Gabrieli S, Ford JM. Default Mode Network Activity and Connectivity in Psychopathology. *Annu Rev Clin Psychol*. 2012;8(1):49-76. doi:10.1146/annurev-clinpsy-032511-143049.
36. Satterthwaite TD, Cook PA, Bruce SE, et al. Dimensional depression severity in women with major depression and post-traumatic stress disorder correlates with fronto-amygdalar hypoconnectivty. *Mol Psychiatry*. 2016;21(7):894-902. doi:10.1038/mp.2015.149.
37. Lecrubier Y, Sheehan D V., Weiller E, et al. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: Reliability and validity according to the CIDI. *Eur Psychiatry*. 1997;12(5):224-231. doi:10.1016/S0924-9338(97)83296-8.
38. First MB et, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV).*; 1997.
39. Avants BB, Epstein CL, Grossman M, Gee JC. Symmetric diffeomorphic image registration with cross-correlation: Evaluating automated labeling of elderly and neurodegenerative brain. *Med Image Anal*. 2008;12(1):26-41. doi:10.1016/j.media.2007.06.004.
40. Klein A, Andersson J, Ardekani BA, et al. Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. *Neuroimage*. 2009;46(3):786-802. doi:10.1016/j.neuroimage.2008.12.037.
41. Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res*. 1996;29(3):162-173. doi:10.1006/cbmr.1996.0014.
42. Greve DN, Fischl B. Accurate and robust brain image alignment using boundary-based registration. *Neuroimage*. 2009;48(1):63-72. doi:10.1016/j.neuroimage.2009.06.060.
43. Jo HJ, Gotts SJ, Reynolds RC, et al. Effective preprocessing procedures virtually eliminate distance-dependent motion artifacts in resting state FMRI. *J Appl Math*. 2013;2013. doi:10.1155/2013/935154.
44. Satterthwaite TD, Elliott MA, Gerraty RT, et al. An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. *Neuroimage*. 2013;64(1):240-256. doi:10.1016/j.neuroimage.2012.08.052.
45. Behzadi Y, Restom K, Liau J, Liu TT. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *Neuroimage*. 2007;37(1):90-101. doi:10.1016/j.neuroimage.2007.04.042.
46. Power JD, Mitra A, Laumann TO, Snyder AZ, Schlaggar BL, Petersen SE. Methods to detect, characterize, and remove motion artifact in resting state fMRI. *Neuroimage*. 2014;84:320-341. doi:10.1016/j.neuroimage.2013.08.048.
47. Nichols TE. Notes on Creating a Standardized Version of DVARS. 2017;(July 2006):1-5. http://arxiv.org/abs/1704.01469.
48. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc*. 1995;57(1):289-300. doi:10.2307/2346101.
49. Satterthwaite TD, Vandekar SN, Wolf DH, et al. Connectome-wide network analysis of youth with Psychosis-Spectrum symptoms. *Mol Psychiatry*. 2015;20(12):1508-1515. doi:10.1038/mp.2015.66.

Figure 1. Data driven multi-dimensional matrix regression (MDMR) analysis revealed four regions with whole-brain connectivity patterns significantly associated with p factor scores: two adjacent parcels of the left middle occipital gyrus (left panel), left lingual gyrus (middle panel), and right middle occipital gyrus (right panel). These four clusters are projected onto a surface volume for visualization.

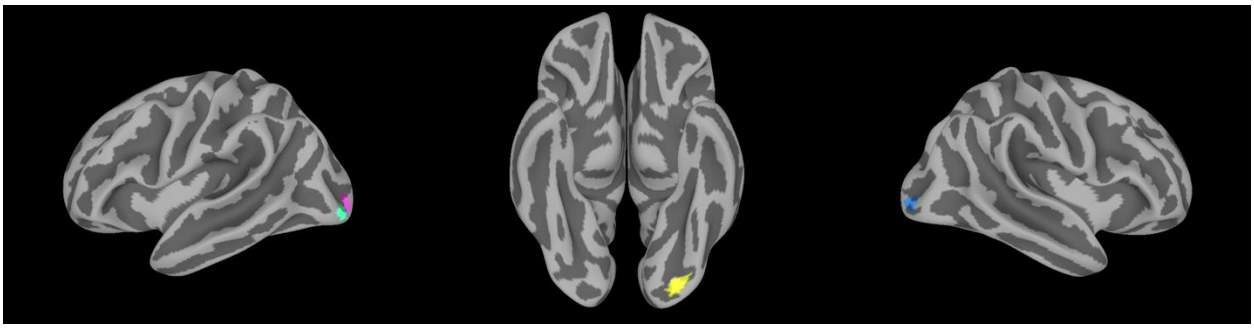

Figure 2. Follow-up connectivity analyses of the four seeds identified through MDMR revealed a highly-conserved pattern of altered connectivity between visual association cortex and both frontoparietal and default mode networks as a function of p factor scores. All results were projected from the volume onto a surface to aid visualization. Left panel: MDMR derived seed regions. Middle panel: average intrinsic connectivity for each seed. Right panel: connectome wide intrinsic connectivity patterns for each seed as a function of p factor scores.

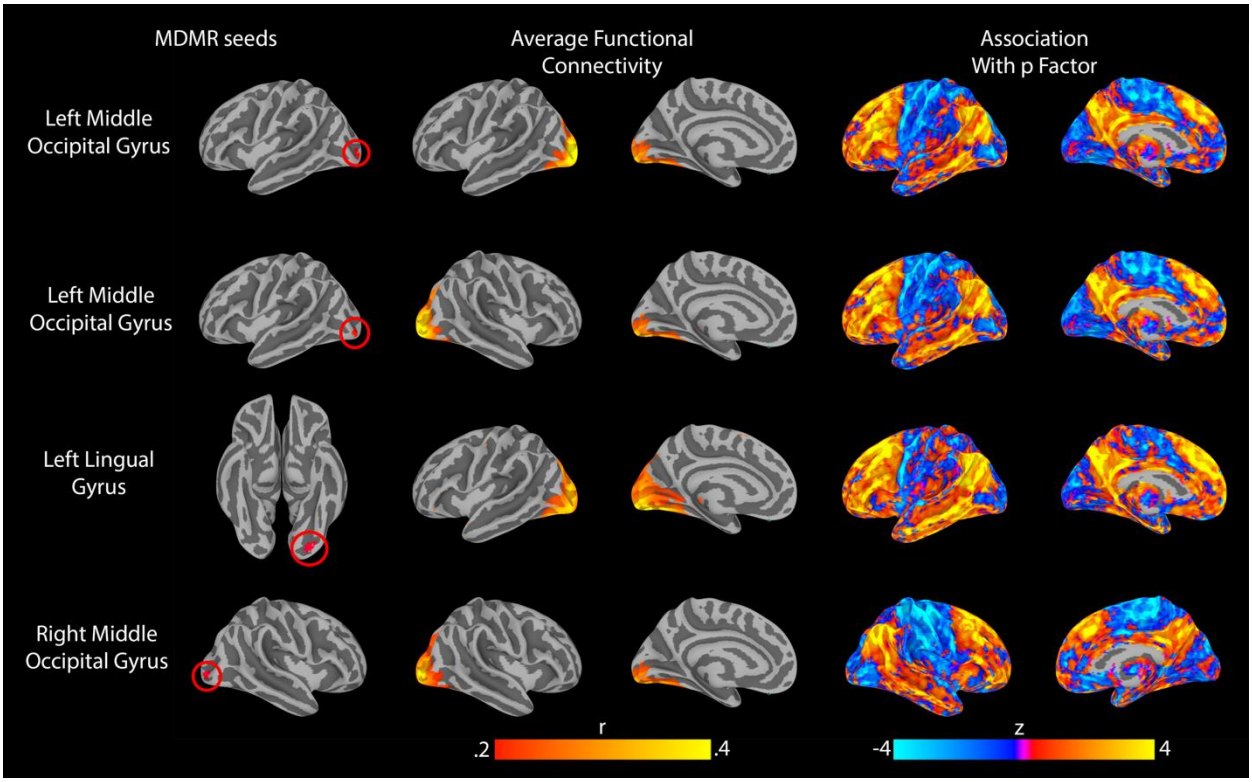

Figure 3. Mean pattern of intrinsic connectivity as a function of p factor scores across the networks associated with each of the four MDMR-derived seeds in visual association cortex (left panel). The relative contributions of seven canonical intrinsic cerebral networks[21] to this mean pattern of connectivity (right panel).