Global connectivity of the frontoparietal cognitive control network is related to depression symptoms in undiagnosed individuals

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ABSTRACT
We all vary in our mental health, even among healthy (undiagnosed) individuals. Understanding this variability may reveal factors driving the onset of mental illness, as well as factors driving sub-clinical mental health problems that can still influence quality of life. To better understand the large-scale brain network mechanisms underlying this variability in mental health we examined the relationship between mental health symptoms and resting-state functional connectivity patterns in cognitive control systems. The frontoparietal cognitive control network (FPN) consists of flexible hubs that can regulate distributed systems depending on current goals, and dysfunction in the FPN has been identified in a variety of psychiatric disorders. Alterations in FPN connectivity may influence mental health by disrupting the ability to regulate symptoms in a goal-directed manner. This suggests that the FPN may play an important role in the promotion and maintenance of mental health generally. Here we test the hypothesis that disruptions in FPN connectivity are related to mental health (depression) symptoms even among healthy individuals. This hypothesis is consistent with a general role of FPN in the regulation of mental health symptoms. We found that depression symptoms were negatively correlated with between-network global connectivity (BGC) of the FPN as well as the default mode network (DMN). This suggests that decreased connectivity between the FPN (and, separately, DMN) and the rest of the brain is related to increased depression symptoms among undiagnosed individuals. These findings complement previous clinical studies to support the hypothesis that global FPN connectivity contributes to the regulation of mental health symptoms across both mentally healthy and unhealthy individuals.

1. INTRODUCTION

Individuals vary in their degree of mental health. Indeed, individuals who have not been diagnosed with a particular disorder can still experience a number of symptoms associated with that disorder. Here we use this natural variability in mental health symptoms in healthy (undiagnosed) individuals to better understand neural factors potentially contributing to day-to-day experiences of poor mental health, as well as factors that may lead to the eventual onset of mental illness. We hypothesized that the variability observed in mental health symptoms among individuals is due in part to the efficacy of the frontoparietal cognitive control network (FPN), based on our previously-developed theoretical proposal that the FPN plays a domain-general protective role against mental health symptoms (Cole et al., 2014).

The proposed theoretical framework suggests that alterations in FPN function may play a common role in multiple mental disorders by disrupting a domain-general cognitive control feedback mechanism that can regulate symptoms when they are experienced (Cole et al., 2014). The FPN is a candidate network for this function because it is a flexible hub, meaning it has a high degree of connectivity across the brain (Cole et al., 2010; Power et al., 2011) and can rapidly modify functional connections according to current goals (Cole et al., 2013). Also supporting this framework, there is strong evidence that these FPN functions are domain general (Chein and Schneider, 2005; Cole et al., 2013; Dosenbach et al., 2007), such that individual differences in the general ability to regulate cognition can influence symptoms. Finally, alterations in FPN functional connectivity (FC) have been identified in a number of mental disorders, consistent with FPN FC being important not just for domain-general cognitive regulation in healthy individuals but also the regulation of symptoms across a variety of mental illnesses. Mental illnesses with observed alterations in FPN FC include: depression (Kaiser et al., 2015), anxiety (Sylvester et al., 2012), Schizophrenia (Cole et al., 2011; Fornito et al., 2011), attention deficit hyperactivity disorder (Li et al., 2014; Park et al., 2016), and eating disorders (Boehm et al., 2014; Cowdrey et al., 2014). Consistent with most of these studies, we focus here on FC measured using functional magnetic resonance imaging (fMRI), calculated as the temporal correlation in the blood oxygenation level dependent (BOLD) signal between brain regions (Biswal et al., 1995) while participants rest in the scanner.

Consistent with the flexible hub framework, a number of studies using different measures have provided converging evidence that the FPN is especially well connected to the rest of the brain. Buckner and colleagues (Buckner et al., 2009) calculated the degree centrality for each voxel in the brain, finding a large number of strong functional connections within the FPN and DMN. Similar results have been observed when the mean FC value is calculated for the connections between each brain region and the rest of the brain (termed global brain connectivity) (Cole et al., 2010). Both of these studies calculated a summary statistic reflecting the degree of connectivity across the whole brain. However, these estimates can be influenced by the relative size of different networks. For example, nodes of a larger network will have a larger overall number of strong

connections than nodes of a smaller network simply because, by definition, within-network connections are stronger on average than between-network connections (Power et al., 2013; Wig et al., 2011). Therefore, we estimated how well each region of the brain was connected to the rest of the brain using between-network global connectivity (BGC), a measure that is not influenced by the size of a network.

Particularly important for our specific test of the flexible hub framework here, patients diagnosed with major depression exhibit differences in FC patterns throughout the brain, including FPN functional connections (Brakowski et al., 2017). Specifically, connectivity within the FPN is decreased in depressed individuals (Alexopoulos et al., 2012), as well as in undiagnosed individuals experiencing a number of depression symptoms relative to individuals not experiencing depression symptoms (Wei et al., 2014). However, Wei and colleagues (Wei et al., 2014) looked at FC with specific seed regions, not global connectivity, in their sample. Another study found that the mean across all brain-wide FC values for each region (i.e., global brain connectivity) was decreased in the medial prefrontal cortex and the dorsolateral prefrontal cortex (dlPFC) portions of the FPN in depressed patients relative to controls (Murrough et al., 2016). Decreases in within-network FPN connectivity have also been observed in a group of individuals reporting depression symptoms in the absence of a clinical diagnosis relative to controls (Hwang et al., 2015). These results suggest that individuals diagnosed with depression are characterized by changes in network-level connectivity that involves the FPN. These previous results are broadly consistent with our hypothesis, yet the extension of results to test whether FPN BGC is related to mental health symptoms among healthy individuals would provide important new evidence for the general (and prodromal) nature of FPN's role in regulating mental health.

Consistent with our previously-developed theoretical framework (Cole et al., 2014) along with observed FPN FC alterations in patients with major depression, we hypothesized that individual differences in depression symptoms in undiagnosed individuals would be correlated with BGC in the FPN. Support for our hypothesis would provide important evidence for a potentially general role of global FPN intrinsic FC in facilitating the regulation of mental health symptoms.

2. METHODS

2.1 Participants

Data were collected at the Rutgers University Brain Imaging Center (RUBIC). The participants were recruited from the Rutgers University-Newark campus and surrounding community. All participants provided informed consent. We collected data from 106 participants. Technical error or equipment malfunction during the scanning session resulted in removing six participants from the study. Four participants were removed from the study because they did not complete the Center for Epidemiological Studies Depression Scale (CESD) during a behavior-only session separate from the MRI session. Studies have proposed that the CESD can be broken down into between one and four factors (Cole et al., 2004; Herrero and Meneses, 2006). In addition to calculating the raw

CESD score for each participant we also calculated three factor scores: somatic symptoms, negative affect, and anhedonia, based on a recent study (Carleton et al., 2013). Participants also completed several measures of flexible cognition during the behavior-only session. These measures included Raven's progressive matrices (Bilker et al., 2012), Cattell's culture fair test (Cattell and Horn, 1978), and Duncan's goal neglect task (Dumontheil et al., 2011). The final sample consisted of 96 participants (42 males, Mean age = 22.06, SD = 3.84).

2.2 MRI Parameters

Multiband whole-brain echo-planar imaging (EPI) acquisition was collected using a 32-channel head coil on a 3T Siemens Trio MRI scanner with the following parameters: TR = 785 ms, TE = 34.8 ms, flip angle = 55°, Bandwidth 1924/Hz/Px, in-plane FoV read = 208 mm, 72 slices, 2.0 mm isotropic voxels, with a multiband acceleration factor of 8. Whole-brain high-resolution T1-weighted and T2-weighted anatomical scans with 0.8 mm isotropic voxels were also collected. Spin echo field maps were collected in both the anterior to posterior direction and the posterior to anterior direction consistent with the Human Connectome Project preprocessing pipelines (Glasser et al., 2013). The resting-state fMRI scan was 14 minutes (1070 TRs) in duration.

2.3 fMRI Preprocessing

Functional imaging data were preprocessed using the Human Connectome Project minimal preprocessing pipeline version 3.5.0. Preprocessing consisted of anatomical restructuring and segmentation, EPI reconstruction, segmentation, and spatial normalization to a standard template, intensity normalization, and motion correction (Glasser et al., 2013). All further processing was conducted in CIFTI 64k greyordinate standard space. The data were parcellated into 360 regions described previously (Glasser et al., 2016), taking the average time series of the vertices within a parcel. At this point all subsequent data analysis was conducted in MATLAB R2014b (The Mathworks). We performed nuisance regression using 12 motion parameters, ventricle and white matter timeseries (as well as their first derivatives), and global signal. We also performed motion scrubbing (Power et al., 2012) based on framewise displacement. Framewise displacement was calculated as the amount of head movement for each frame relative to the previous in terms of Euclidean distance. We next applied a low pass temporal filter (0.3 Hz) to the framewise displacement vector in order to reduce the effect of respiration on our framewise displacement measure (Siegel et al., 2016). The framewise displacement threshold for motion scrubbing was set at 0.3 mm. Motion scrubbing consisted of removing the flagged frame from the timeseries as well as one frame prior and the two frames following. FC was estimated by calculating the Pearson correlation of the BOLD timeseries between each pair of the parcels defined by Glasser and colleagues (Glasser et al., 2016).

2.4 Network Assignment and Analysis

The network assignment of each of the parcels was completed on an independent dataset, the Human Connectome Project (100 unrelated) (Van Essen et al., 2013). Briefly, each parcel was assigned to a network using the Generalized Louvain method for community detection (Ito et al., 2017). This process was conducted using resting-state data. We identified 14 functional networks (See Figure 1). The functional network topology findings replicate the major features of several previously published network partitions (Gordon et al., 2016; Power et al., 2011; Yeo et al., 2011).

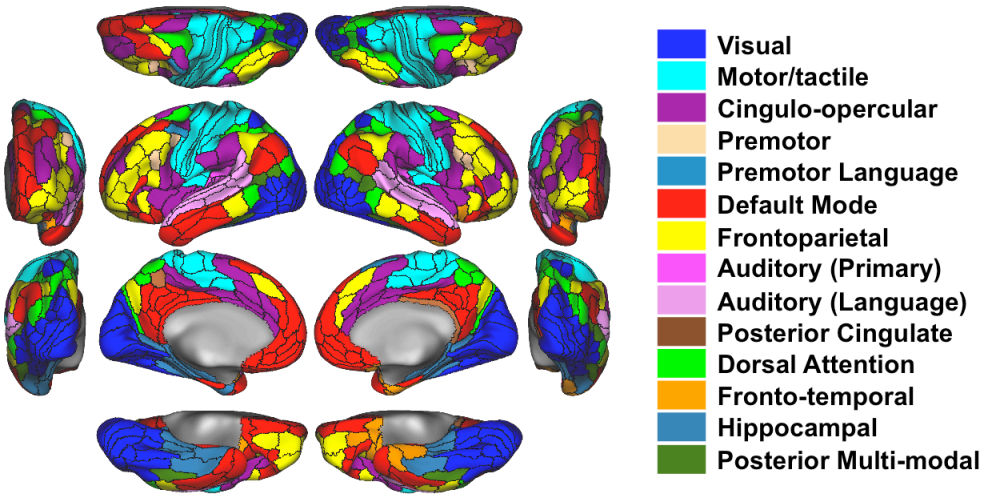

Figure 1 - Network assignment. Resting-state fMRI data from an independent dataset (HCP: 100 unrelated) was used to assign each parcel to a network using a community detection algorithm. This resulted in 14 total networks. Color indicates the network assignment for each parcel.

We were interested in the relationship between the frequency at which participants experienced depression symptoms and the degree of between-network global connectivity (BGC). Specifically, we were interested in a measure that would estimate the strength of FC for each region of a network to all of the other regions in different networks. BGC was calculated for each region individually and defined as the mean FC for all out-of-network connections. Out-of-network connections were defined as all connections from a source region to target regions outside the source region's network. This process was completed for all regions until we had a BGC value for each region in the brain. Then we calculated the mean BGC value for each of the functional networks to summarize effects at the network level.

More formally, BGC was defined for each region as:

$$BGC_i = \frac{\sum_{j \notin C} W_{ij}}{N_{total} - N_C}$$

where BGC_i corresponds to the out-of-network weighted degree of region i in network C, $j \notin C$ corresponds to all regions not in network C, W_{ij} corresponds to the FC estimate between regions i and j, N_{total} corresponds to the total number of regions, and N_C corresponds to the total number of regions in network C.

We tested the relationship between BGC and depression symptoms in all brain networks. Due to the large number of statistical tests we report the false-discovery rate (FDR)-corrected *p*-values for primary analyses (Benjamini and Hochberg, 1995). Our main hypothesis was that BGC in the FPN was correlated with depression symptoms. Because this was a primary hypothesis we report the uncorrected p-value. Although it should be noted that this comparison was also significant when corrected for multiple comparisons (See Results). Follow-up and control analyses were not independent of the primary tests and are not corrected.

3. RESULTS

3.1 Depression Symptom Scores

We hypothesized that the frequency of experiencing depression symptoms are related to individual differences in the between-network global connectivity of the FPN. This would be consistent with the involvement of FPN in domain-general cognitive regulation, broadly construed to include emotion (Cole et al., 2014). We used a standard measure of depression symptoms, the CESD, to measure the frequency of depression symptoms. CESD scores (*M = 17.41, SD = 9.26*) varied from a minimum of 0 to a maximum of 43 (out of a possible 60). The characteristics of our sample were consistent with previous studies using the CESD with undiagnosed young adults (Gress-Smith et al., 2015; Van Dam and Earleywine, 2011). However, the scores were not normally distributed based on a Kolomogorov–Smirnov test ($p < 0.023$). We therefore used the Box-Cox power transformation (Box and Cox, 1964), a common approach to correct for non-normality. After the transformation the data no longer deviated from a normal distribution ($p = 0.17$). The transformed data were used for all subsequent analyses. CESD scores were not correlated with any of the flexible cognition measures (*smallest p = 0.28*).

We also calculated CESD sub-scores for somatic, negative affect, and anhedonia factors. After Box-Cox transformation none of the factor score distributions significantly deviated from a normal distribution (*somatic p = 0.4, negative affect p = 0.19, anhedonia p = 0.056*). All three of the factors were significantly correlated with the overall CESD scores (*somatic r = 0.77, uncorrected p < 0.001; negative affect r = 0.80, uncorrected p< 0.001; anhedonia r = 0.52, uncorrected p < 0.001*, See Table 1). The three factors were also correlated with each other (*correlation between somatic and negative affect r = 0.55, correlation between somatic and anhedonia r = 0.18, correlation between negative affect and anhedonia r = 0.26*, See Table 1). Although all of the factors were highly related to the overall CESD score, they appear to have contributed unique variance as the highest correlation between any two factors was only accounting for 30% of the variance (based on R^2 values).

Table 1. Correlation between the CESD and CESD factors

	Overall CESD	Somatic	Negative Affect	Anhedonia
Overall CESD	-----	-----	-----	-----
Somatic	0.77	-----	-----	-----
Negative Affect	0.80	0.55	-----	-----
Anhedonia	0.52	0.18	0.26	-----

3.2 Between-Network Global Connectivity

We calculated BGC values using resting-state fMRI data for each functionally defined cortical parcel (Figure 2). DMN regions tended to have lower BGC values, consistent with Power et al. (Power et al., 2011). In contrast, the FPN had high levels of BGC in lateral prefrontal portions of the network ($M = 0.004, SD = 0.02$) relative to the mean of regions outside of the FPN ($M = -0.0083, SD = 0.013; t(190) = 4.7, p < 0.0001$). However, FPN had lower BGC values in parietal ($M = -0.0341, SD = 0.0243$), inferior frontal ($M = -0.0228, SD = 0.0196$) and temporal lobe regions of the network ($M = -0.0417, SD = 0.0218$) relative to the mean of regions outside of the FPN (*largest* $p < 0.0001$). Sensory networks exhibited two patterns. The visual network had some of the lowest BGC values in the brain with the primary visual cortex region showing the least BGC in the network ($M = -0.0742, SD = 0.0348$). In contrast, the auditory network ($M = 0.0276, SD = 0.0225$) and portions of the sensorimotor network surrounding the central sulcus ($M = 0.0117, SD = 0.0249$) both showed a high degree of BGC. The sensorimotor regions closest to the central sulcus showed more moderate BGC scores ($M = -0.0139, SD = 0.0289$).

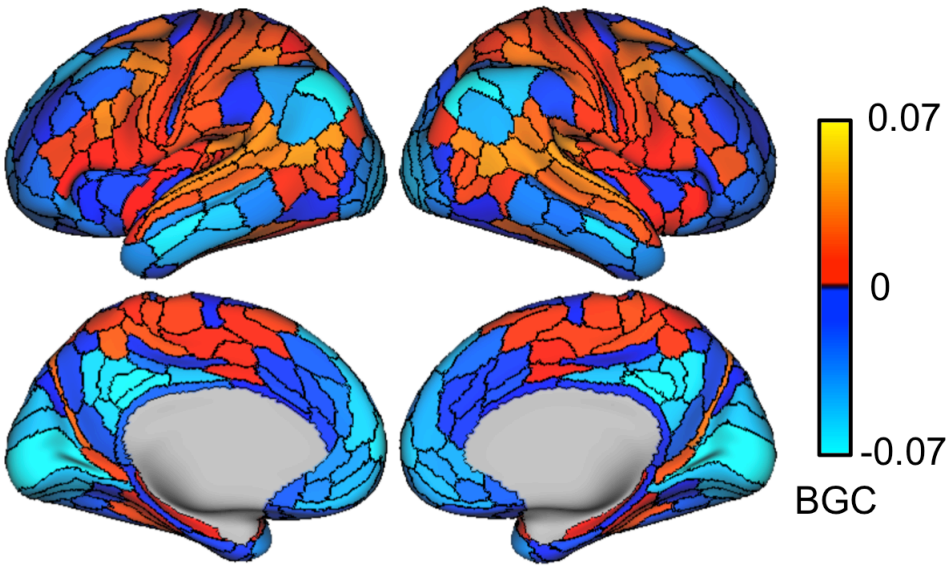

Figure 2 – Between network global connectivity across all cortical regions. Between network global connectivity for region A is defined as the mean FC (Pearson correlation) between that region A and all other regions outside of region A's network. Warm values indicate positive values and cool values indicate negative values.

3.3 Correlation Between BGC and Depression Symptoms

We next tested for a relationship between BGC and depression symptoms. This involved creating a mean BGC score for each functional network and testing for correlation between those values and the depression symptom measure (See Table 2). Consistent with our hypothesis, we found that FPN BGC was significantly correlated with depression symptoms (*r = -0.262, p = 0.009, FDR adjusted for multiple comparisons p = 0.044*) (Figure 3A). Unexpectedly, we found that DMN BGC was also significantly correlated with depression symptoms (*r = -0.25, FDR adjusted p = 0.049*) (Figure 3B). These findings suggest that greater FC between the FPN and the rest of the brain (outside of the FPN) is related to less frequent depression symptoms. Less depression symptoms are also related to greater FC between DMN regions and the rest of the brain (outside of the DMN). We additionally found significant negative correlations between BGC and depression symptoms in two small networks: a premotor language network (*r = -0.287, FDR adjusted p = 0.03)*, and a separate premotor network (*r = -0.296, FDR adjusted p = 0.03*).

Table 2. Correlation between BGC and CESD scores

Network	Pearson's r	FDR adjusted p-value
Visual	0.030	0.831
Motor/tactile	-0.179	0.189
Cingulo-opercular	-0.156	0.239
Premotor	-0.296	0.032*
Premotor Language	-0.287	0.032*
Default Mode	-0.250	0.049*
Frontoparietal	-0.262	0.044*
Auditory (Primary)	-0.008	0.938
Auditory (Language)	-0.214	0.102
Post. Cingulate	0.079	0.565
Dorsal Attention	-0.057	0.678
Fronto-temporal	0.104	0.439
Hippocampal	-0.134	0.300
Post. Multi-modal	-0.153	0.239

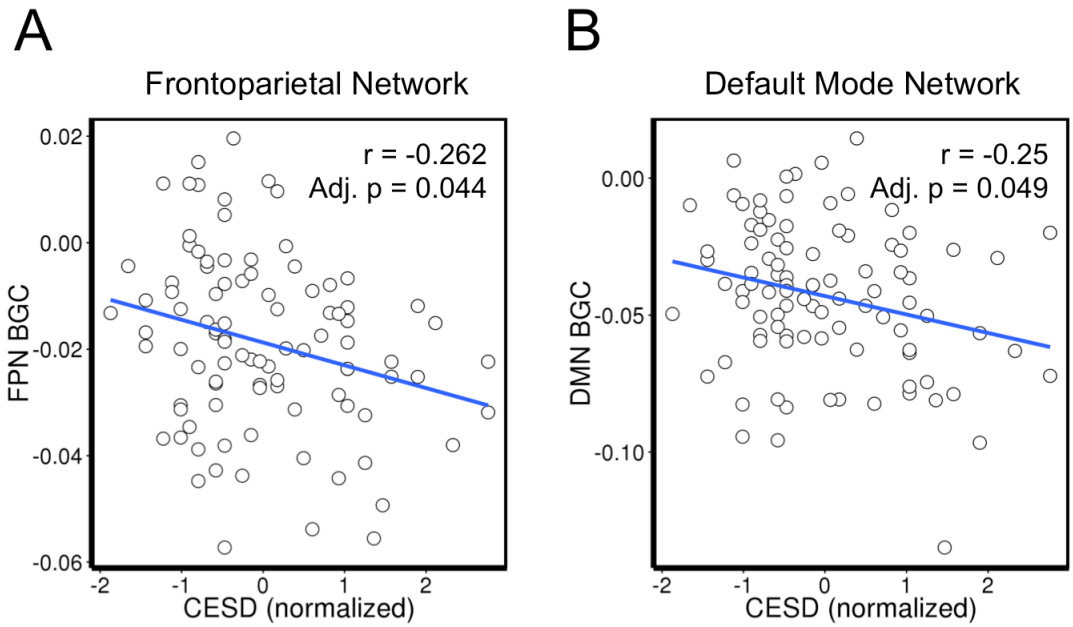

Figure 3 –CESD scores and BGC in the FPN and DMN are negatively correlated. A) Between-network global connectivity in the FPN is plotted on the y-axis and CESD scores are plotted on the x-axis. B) Between-network global connectivity in the DMN is plotted on the y-axis and CESD scores are plotted on the x-axis.

In order to verify that these correlations were not dependent on the Box-Cox transformation we used to normalize the depression symptom data we also ran non-parametric Spearman's rank correlations, which do not require normally distributed data. Our conclusions based on $p < 0.05$ (uncorrected for multiple comparisons) remained unchanged. Specifically, the BGC-depression rank

correlations were consistent with significant Pearson correlations: FPN (*rho = -0.247, p = 0.015*), DMN (*rho = -0.223, p = 0.029*), unknown-premotor network (*rho = -0.236, p = 0.02*), and FPN-premotor network (*rho = -0.254, p = 0.013*).

Next, we tested if the relationships between BGC and overall depression scores were driven by specific depression factors. We tested for correlation between the BGC values and three factors derived from the CESD questionnaire: somatic symptoms, negative affect, and anhedonia symptoms (Carleton et al., 2013). In the FPN, BGC was only significantly correlated with anhedonia symptoms (*r = -0.25, p = 0.014*). FPN BGC was only marginally correlated with somatic symptoms (*r = -0.18, p = 0.07*) and not significantly correlated with negative affect (*r = -0.16, p = 0.12*). In the DMN, BGC was only marginally significantly correlated with somatic symptoms (*r = -0.18, uncorrected p = 0.07*) and anhedonia symptoms (*r = -0.19, p = 0.058*), and not significantly correlated with negative affect (*r = -0.13, p = 0.21*).

3.4 Observed BGC-depression Correlations were not Dependent on Connections Between FPN and DMN

The magnitude and direction of the BGC-depression correlations were similar for the FPN and DMN. One possible explanation for these results is that the observed BGC-depression effects for both networks were driven primarily by the FC between the FPN and DMN. We tested this possibility by recalculating BGC for the FPN by excluding connections to the DMN, and by recalculating BGC for the DMN by excluding the connections to the FPN. This approach minimizes the possibility that connections between these networks drove the original correlations between depression symptoms and BGC. The magnitude and direction of the correlations between depression symptoms and BGC in the FPN (*r = -0.239, uncorrected p = 0.02*) and the DMN (*r = -0.245, uncorrected p = 0.016*) were similar when we excluded the connections between FPN and DMN from the BGC calculation. This suggests the original BGC-depression correlations were not dependent on FPN-DMN connections.

3.5 Within Network Connectivity does not Correlate with Depression Symptoms

We focused on between-network connectivity, yet the degree of connectivity within a functional network might also be related to depression symptoms. For example, a high degree of FC within a network may reflect more homogeneous network activity. In this case the network would be tightly coupled and all of the component regions would likely be serving a very similar function. However, a lower degree of FC within a network may reflect more heterogeneous processing. In this case the different regions of a functional network may all be involved in the same general process, but they may be contributing in different ways. These differences in within-network functionality may, in turn, relate to depression symptoms.

Consistent with our choice to focus primarily on between-network effects, within-network FC in the FPN was not significantly correlated with depression symptoms (*r = 0.02, p = 0.85*). Within-network FC in the DMN was also not

significantly correlated with depression symptoms ($r = 0.15, p = 0.13$). However, there was a significant difference in the DMN correlation coefficients comparing BGC ($r = -0.25$) and within-network connectivity ($r = 0.15$) with depression symptoms ($z = 2.8, p = 0.005$). It will be important for future studies to test this effect for replication, given the non-significance of the DMN within-network FC-depression effect relative to a correlation of 0.

4. DISCUSSION

Based on convergent evidence across a variety of mental illnesses we predicted that individual differences in FPN global connectivity would be correlated with many mental illness symptoms (Cole et al., 2014). This is consistent with extensive evidence that the FPN is a domain-general cognitive control system that regulates general goal pursuit processes (Cole and Schneider, 2007; Duncan, 2010; Schneider, 2003), including regulation of mental illness symptoms (Cole et al., 2014). We sought to expand the general relevance of this framework by including mental illness symptoms experienced in everyday life. This involved investigating the relationship between the symptoms of major depression, one of the most commonly experienced set of symptoms (Centers for Disease Control and Prevention (CDC), 2010), and FPN global connectivity properties. We further ensured the general relevance of the findings by focusing on undiagnosed individuals who (unlike comparisons between psychiatric patients and healthy controls) varied naturally in their depression symptoms and primarily experienced them in the normal (i.e., sub-clinical) range.

As predicted, we found a significant relationship between how well-connected the FPN was to the rest of the brain and the frequency of depression symptoms in undiagnosed adults. A similar relationship was also identified for DMN, which has been linked to rumination symptoms of depression (Hamilton et al., 2011). We used BGC to estimate the degree of brain-wide connectivity for each brain region. BGC was used in order to reduce the influence of network size on global connectivity estimates, which is a problem for the most common graph centrality measures (e.g., degree centrality) (Power et al., 2013). The results suggest that individuals who report less frequent depression symptoms in everyday life are characterized by a FPN and DMN that are more connected to the rest of the brain. This appears to be a global connectivity effect, as the direct connections between the FPN and DMN are not driving the relationship between BGC and depression symptoms. These results strongly support our previously developed theoretical framework, suggesting natural variance in FPN global connectivity likely influences each individual's ability to regulate mental health symptoms (here, depression) in everyday life.

4.1 Between-network global connectivity identifies how well each brain region is connected to other brain networks

We hypothesized that individuals exhibiting greater FC between the FPN and the rest of the brain would report experiencing depression symptoms less frequently. We used BGC, a measure that calculates the mean FC between each brain region and all other out-of-network brain regions (Ito et al., 2017) to

evaluate this hypothesis. BGC reduces the potential bias of other graph centrality measures, which can be inflated in regions assigned to large networks (Power et al., 2013). Using global brain connectivity (the mean FC for each region including within network connections) results in many DMN regions showing high connectivity with the rest of the brain (Cole et al., 2010; Liang et al., 2013). Using the graph theoretic measure of degree, which counts the number of connections for each voxel with any other voxel in the brain also results in high estimates of connectivity for the DMN (Buckner et al., 2009). However, we found that BGC was relatively low in the DMN. This is consistent with studies using participation coefficient (the proportion of between-network vs. within-network connectivity), which also found low centrality of DMN regions (Power et al., 2013, 2011). Together with the fact that DMN is the largest cortical network in the brain, these results suggest that the previous findings identifying the DMN as highly connected to the rest of the brain are largely driven by high FC within the DMN, and do not necessarily reflect greater connectivity between the DMN and nodes in other functional networks.

The results we observed with BGC were similar to previous attempts to identify hubs and the most well connected regions in the brain. BGC was high in the lateral prefrontal cortex, the motor and tactile cortex, the primary and language portions of the auditory cortex, and higher order visual regions. Lateral prefrontal regions and higher order visual areas show a greater degree of FC (Buckner et al., 2009) and a higher global brain connectivity (Cole et al., 2010). Another study examining global brain connectivity also found higher values in the lateral prefrontal cortex, higher order visual regions, auditory cortex, and somatosensory cortex (Liang et al., 2013). Local and distant connectivity has been found to be higher in lateral prefrontal regions and auditory cortex, while local connectivity is higher in somatomotor cortex (Sepulcre et al., 2010). We observed that the level of BGC was consistent with previous attempts to classify the degree of connectivity in many brain regions.

There were also some discrepancies between previous methods and BGC. We found that BGC was quite low in lower visual regions in contrast to higher connectivity estimates calculated by others (Cole et al., 2010; Liang et al., 2013). The differences observed between BGC and other measures of connectivity strength may be driven by BGC not considering the relatively strong local connections within the visual network. In fact, primary and secondary visual cortex show high local connectivity relative to distant connectivity strength (Sepulcre et al., 2010). It will be important for future studies to identify whether differences observed in primary sensory cortices are driven by an imbalance between within and between-network connectivity.

4.2 BGC in the FPN and DMN is negatively correlated with depression symptoms

We found that BGC in FPN and DMN showed a significant negative correlation with depression symptom frequency. This suggests that individuals exhibiting greater connectivity of the FPN and the DMN with the rest of the brain experience symptoms of depression less frequently. The correlation between

BGC in the FPN and depression symptoms supports our hypothesis that a well-connected FPN may serve a protective role against mental health symptoms in general, and specifically in this case, depression symptoms (Cole et al., 2014).

Decreases in FPN FC have been reported in individuals diagnosed with major depression (Alexopoulos et al., 2012; Murrough et al., 2016; Veer, 2010). We build on these findings by observing similar results in a variable sample of undiagnosed individuals that likely includes primarily mentally healthy, but also some mentally unhealthy, participants. Another study examining FC in a group of undiagnosed individuals with higher levels of depression symptoms found that connectivity between the superior parietal lobule and the dlPFC portion of the FPN was decreased relative to a group of undiagnosed individuals with fewer depression symptoms (Wei et al., 2014). Undiagnosed participants experiencing more depression symptoms have also been reported to have reduced FC between dlPFC and the supramarginal gyrus, insula, operculum, precuneus and parahippocampal gyrus relative to a group of undiagnosed individuals with fewer depression symptoms (Hwang et al., 2015). Our findings suggest that greater global connectivity of the FPN is related to reduced depression symptoms. Our data regarding global connectivity differences is consistent with a recent study that found reduced global brain connectivity in the lateral PFC in depression patients (Abdallah et al., 2016). Furthermore, following a treatment of ketamine, global brain connectivity in this region increased. The magnitude of this global brain connectivity increase was greatest in patients who reported the greatest reduction in depression symptoms.

We also found a negative correlation between BGC in the DMN and depression symptoms. This finding may reflect an inability for individuals experiencing more depression symptoms to disengage the DMN in situations when attentional or cognitive resources need to be allocated. This interpretation is consistent with another study suggesting that depressed patients are not able to disengage or decrease DMN activity when viewing emotional pictures relative to a control group (Sheline et al., 2009). Depression patients also exhibit decreased FC between the DMN and executive networks like the FPN and dorsal attention network (Abbott et al., 2013; Manoliu et al., 2014). These findings provide further support for the interpretation that depressed individuals may have a difficult time disengaging the DMN because the connections from cognitive control networks to the DMN are decreased.

A number of studies have suggested that FC within portions of the DMN is increased in depression patients (Greicius et al., 2007; Li et al., 2013). Although we did not find a significant correlation between within-network FC in the DMN and depression symptoms, we did see a trend toward a positive correlation. Our lack of a correlation between within-network FC in the DMN and depression symptoms could be due to methodological differences in using undiagnosed individuals versus comparing a control group to a group diagnosed with depression. Additionally, we considered the entire DMN rather than using a seed correlation approach or further partitioning the DMN. It will be important for future studies to investigate the relationship between within-DMN FC and depression

symptoms, verifying this effect in a larger sample and tying it to specific neural mechanisms and specific depression symptoms (e.g., rumination).

5. Conclusion

The current study sought to test our previously-developed framework that suggests FPN (along with other cognitive control networks) acts as a protective factor against mental disease via its widespread FC with other networks (Cole et al., 2014). Consistent with this, we identified a negative correlation between depression symptoms and a measure of between-network, global FC in the FPN (and DMN) in a sample of undiagnosed individuals. These results suggest the human brain's global network architecture is critical for maintaining mental health even in undiagnosed individuals, supporting the possibility that FPN maintains a goal-directed feedback loop to regulate symptoms as they arise. It will be important for future research to characterize the exact mechanisms by which FPN influences symptoms, and to assess the possibility of enhancing FPN FC in the interest of reducing symptoms and potentially preventing the onset of mental illness.

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