A Computational Network Control Theory Analysis of Depression Symptoms

Yoed N. Kenett[1], Roger E. Beaty[2] and John D. Medaglia[3,4]

[1]Department of Psychology, University of Pennsylvania, Philadelphia, PA, USA, [2]Department of Psychology, Pennsylvania State University, University Park, PA, USA, [3]Department of Psychology, Drexel University, Philadelphia, PA, USA and [4]Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Abstract

Rumination and impaired inhibition are considered core characteristics of depression. However, the neurocognitive mechanisms that contribute to these atypical cognitive processes remain unclear. To address this question, we apply a computational network control theory approach to structural brain imaging data acquired via diffusion tensor imaging in a large sample of participants, to examine how network control theory relates to individual differences in subclinical depression. Recent application of this theory at the neural level is built on a model of brain dynamics, which mathematically models patterns of inter-region activity propagated along the structure of an underlying network. The strength of this approach is its ability to characterize the potential role of each brain region in regulating whole-brain network function based on its anatomical fingerprint and a simplified model of node dynamics. We find that subclinical depression is negatively related to higher integration abilities in the right anterior insula, replicating and extending previous studies implicating atypical switching between the default mode and Executive Control Networks in depression. We also find that subclinical depression is related to the ability to "drive" the brain system into easy to reach neural states in several brain regions, including the bilateral lingual gyrus and lateral occipital gyrus. These findings highlight brain regions less known in their role in depression, and clarify their roles in driving the brain into different neural states related to depression symptoms.

CAMBRIDGE
UNIVERSITY PRESS

Depression is attributed to various maladaptive affective and cognitive processes, including atypical cognitive control processes (Rizk et al., 2017). Specifically, impaired inhibition of negative thoughts, also known as rumination, is considered a major symptom in depression (Beck, 1976; Nolen-Hoeksema & Morrow, 1993). However, the precise neurocognitive processes that lead to such atypical inhibition processes are currently debated. This is also the case for the neurocognitive processes related to subclinical levels of depression, which are an important precursor of depression (Li et al., 2015). Here, we apply a state-of-the-art computational approach—network control theory (NCT)—to quantitatively examine how different control strategies in specific brain regions relate to subclinical levels of depression. Such an approach can further elucidate the nature of this atypical inhibition and possibly serve as predictors in the occurrence of Major Depression Disorders (MDD).

In the past few years, a large-scale, whole-brain systems approach has been applied to study psychopathology (Menon, 2011). Such an approach is moving away from examining clinical symptoms and their relation to specific brain regions (such as the amygdala in relation to depression) and is focusing on how such clinical symptoms relate to the interaction between brain regions and networks. Network approaches typically examine the interaction, and dysfunction, of three large-scale networks: The Executive Control Network (ECN), the Default Mode Network (DMN), and the Salience Network (SN). The ECN is a set of prefrontal and posterior parietal regions that are engaged during cognitive tasks that require externally directed attention, such as working memory, relational integration, response inhibition, and task-set switching (Zabelina & Andrews-Hanna, 2016). The DMN is a set of midline and inferior parietal regions that activate in the absence of most external task demands, and is often associated with mind-wandering and other modes of spontaneous thought (Andrews-Hanna, Smallwood, & Spreng, 2014). The SN is a set of cingulate and fronto-insular regions that are involved in detecting, integrating, and filtering relevant interoceptive, autonomic, and emotional information (Seeley et al., 2007; Uddin, 2015).

In line with a network system approach, effort has been made to identify the role of the ECN, DMN, and SN in patients with MDD. Specifically, Cole, Repovš, and Anticevic (2014) proposed a theory that highlighted the significance of ECN global dysconnectivity in mental

disorders such as MDD (Cole, Repovš, & Anticevic, 2014). Recently, Schultz et al. (2018) provided empirical evidence supporting this theory. The authors found a negative relationship between depression symptoms and a measure of global connectivity in the ECN (Schultz et al., 2018). Furthermore, several studies have found atypical activation in the DMN, related to rumination and processing of negative stimuli in patients with MDD (Cooney, Joormann, Eugène, Dennis, & Gotlib, 2010; Hamilton, Chen, & Gotlib, 2013; Hamilton, Chen, Thomason, Schwartz, & Gotlib, 2011; Sheline et al., 2009). For example, Hamilton, Furman et al. (2011) found atypical ECN and DMN activation related to maladaptive rumination processes in patients with MDD (Hamilton, Furman et al., 2011). Finally, increased attention is given to the role of the SN in MDD (Hamilton, Chen, & Gotlib, 2013; Hamilton et al., 2016). This is based on the role of the SN in orienting and responding to stimuli, and its role in switching between the ECN and DMN (Sridharan, Levitin, & Menon, 2008). Such research focuses on the role of the amygdala and the anterior insula in MDD. The amygdala is involved in mnemonic and affective processing, particularly negatively valanced emotions such as fear and anxiety (Calhoon & Tye, 2015). The anterior insula has widespread anatomical connections to cortical and limbic regions and is implicated in the coordination between the ECN and DMN (Iwabuchi et al., 2014; Menon & Uddin, 2010). Importantly, atypical functional activity and connectivity of the anterior insula have been found in several studies in patients with MDD (Iwabuchi et al., 2014). Specifically, the right anterior insula has been implicated in greater levels of maladaptive rumination (Hamilton, Furman et al., 2011), and has been argued to represent a vulnerability marker for depression (Liu et al., 2010).

As such, neuroimaging studies using network methods are elucidating important interactions across different neural systems related to MDD. Functional Magnetic Resonance Imaging (fMRI) is well suited for examining state-level variability across participants, given that rest- and task-based functional activity related patterns fluctuate in ways that predict cognitive measures. However, anatomical brain network analysis may better capture trait level variability across participants, by measuring stable individual differences in their neuroanatomy that might constrain neural and cognitive states. This is due to the unique information embedded in the brain's anatomical network organization, that has been demonstrated to organize much of observable functional activity such as that observed in fMRI (Hermundstad et al., 2013; Hermundstad et al., 2014; Medaglia et al., 2018b). Such information can be measured via diffusion tractography, measuring white matter tract connectivity in typical and clinical populations (Sotiropoulos & Zalesky, 2017).

Indeed, an association between white matter abnormalities and MDD has been established (Sexton, Mackay, & Ebmeier, 2009; White, Nelson, & Lim, 2008). Several studies using diffusion tensor imaging (DTI) have examined whole brain white matter connectivity related to MDD (De Witte & Mueller, 2017; Gong & He, 2015; Griffa, Baumann, Thiran, & Hagmann, 2013; Murphy & Frodl, 2011; Rizk et al., 2017). However, these studies have resulted in conflicting findings, with some reporting MDD-related differences in white matter connectivity (Bai et al., 2012; Korgaonkar, Fornito, Williams, & Grieve, 2014) and others showing no differences (Choi et al., 2014; Qin et al., 2014). Furthermore, most studies of MDD have focused on the amygdala and its connectivity to other brain regions (De Witte & Mueller, 2017). A recent DTI study examined the relationship between

cognitive control processes and white matter integrity in unmedicated young and midlife patients with MDD (Rizk et al., 2017). The authors found that unlike control participants, patients with MDD failed to exhibit an association between Stroop interference and white matter integrity in the anterior cingulate cortex (Rizk et al., 2017). However, the authors argue for the importance of further studies elucidating the relation between white matter integrity and cognitive control mechanisms in patients with MDD.

Thus, individual differences in subclinical levels of depression may be related to variance in whole brain white matter connectivity, which may impact efficient cognitive control processes. However, the current research on the influence of depression on white matter integrity is contradictory and debated (Rizk et al., 2017). This may be due to small sample sizes usually collected in such studies or the focus on white matter integrity, as opposed to white matter connectivity, as related to depression. In the current study, we apply computational NCT in relation to individual differences in subclinical depression. This allows us to computationally examine how whole brain structural connectivity theoretically "controls" dynamic brain processes in relation to individual differences in subclinical depression.

From an engineering perspective, network control is a process in which a system is deliberately shifted or guided along a particular trajectory to support specific goals (Tang & Bassett, 2018). This guidance is usually theoretically examined by simulating injection of signals into the system via deliberate perturbations. Recently, NCT has been applied to study the dynamics of large-scale neural systems (Gu et al., 2015; Medaglia et al., 2016; Yan et al., 2017). For example, Yan et al. (2017) applied NCT to investigate the significance of controllability of specific neurons in *Caenorhabditis Elegans* on its locomotion behavior. Importantly, these predictions were empirically examined and verified by ablating specific neurons identified as significant controllers (Yan et al., 2017), thus demonstrating the feasibility of this computational theoretical approach in examining control strategies and dynamics in such neural systems.

Investigating the controllability of neural dynamics is computationally challenging, requiring to model non-linear neural dynamics and the neural structural connectivity that gives rise to such dynamics (Gu et al., 2015). Thus, a common practice in the general application of NCT is based on linear models of dynamic processes (Liu, Slotine, & Barabási, 2011). Accordingly, the application of control theory in neuroscience is built upon anatomical connectivity networks combined with a simplified, linear model of such neural dynamics (Gu et al., 2015). This assumption of linear dynamics is commonly accepted and is based upon prior models linking anatomical brain networks to resting state functional dynamics (Abdelnour, Voss, & Raj, 2014; Bettinardi et al., 2017; Cole, Ito, Bassett, & Schultz, 2016; Galán, 2008; Honey et al., 2009; Honey, Thivierge, & Sporns, 2010; Muldoon et al., 2016). Importantly, Muldoon et al. (2016) demonstrated how a non-linear computational model of neural dynamics validates controllability measures computed based on the simplified linear model. Thus, while the forefront of computational neuroscience aims to develop methods to map the relation between structural and functional signals (e.g., Medaglia et al., 2018b), controllability measures built on a simplified linear model have proven their fruitfulness.

Recent applications of NCT to neural systems have proposed a set of three controllability metrics that quantify the contributions made by individual brain regions in "driving" the brain network

from one state into another (Gu et al., 2015). Here, "state" refers to the magnitude of neurophysiological activity across brain regions at a single time point. *Average controllability* quantifies the theoretical extent to which a specific brain region can easily "drive" the brain into easy to reach states with little energy and has been observed in DMN regions (Gu et al., 2015; Pasqualetti, Zampieri, & Bullo, 2014). *Modal controllability* quantifies the theoretical extent to which a specific brain region can easily "drive" the brain into states that require a substantial amount of energy, or are difficult to reach states, and has been observed in fronto-parietal regions (Gu et al., 2015). *Boundary controllability* quantifies the theoretical extent to which a specific brain region lies at the "boundary" between network sub-communities, contributing to the integration between them. Brain regions with high boundary controllability have been associated with attention systems (Gu et al., 2015). Together, these three control roles define different continua in brain networks: Brain regions may vary in their tendency to drive the brain to or away from specific types of states or into integrated or segregated states. However, these measures are mathematical abstractions and the significance of these measures in studying behavior is still open. A growing number of studies is, however, currently establishing a link between NCT and cognition (Kenett et al., 2018; Medaglia et al., 2016; Medaglia et al., 2018a; Tang et al., 2017).

A few recent studies have demonstrated the feasibility of applying NCT to study cognition. Medaglia et al. (2016) related modal and boundary controllability to performance on a variety of tasks that demand executive control (such as the Stroop task), and it is the first to ground cognitive control in network controllability measures. Tang et al. (2017) investigated whole brain network controllability measures related to typical neurocognitive development. The authors found that the relative strength of average controllability of subcortical brain regions predicted improved cognitive performance as related to development. Kenett et al. (2018) applied NCT to examine differences in controllability measures across the whole brain related to intelligence and creativity. The authors found a positive relation with average controllability and intelligence, and a positive relation with modal controllability and creativity across different brain regions (Kenett et al., 2018). The authors also find opposite relations between boundary controllability, intelligence, and creativity. Thus, different controllability measures across different brain regions can be related to cognitive processes in typical populations. Recently, Jeganathan et al. (2018) applied NCT analysis on a sample of participants with bipolar depression and participants that are in high risk of bipolar depression. The authors found decreased average controllability in both of these groups compared with controls in several brain regions including the right inferior frontal gyrus, insula, and the pre-central gyrus (Jeganathan et al., 2018).

Thus, the application of NCT in neurocognitive research advances our understanding of regions' theoretical roles in driving activity across the brain as related to cognitive processes in typical and clinical populations. In the current study, we apply NCT to white matter anatomical connectivity networks in a large sample of participants ($N = 349$) who were assessed for subclinical depressive symptoms. For each participant, we extracted anatomical connectivity matrices based on diffusion tractography, and computed average, modal, and boundary controllability for regions across the whole brain. We then examined and compared the relation of each of the controllability measures to the depression measure. This allows us to quantitatively examine theories on the roles of the ECN, DMN, and SN regions in driving brain network dynamics as related to subclinical depression. While we are theoretically motivated to focus on these network systems, we conduct a whole-brain analysis to examine differences in controllability across all possible brain regions. This is motivated by the possibility that different brain regions actually regulate such dynamics, whereas functional imaging studies are the consequences of underlying dynamic-driving roles across the brain. In line with studies that have revealed atypical hyper activity and connectivity within the ECN and DMN, we expected to find higher average controllability in brain regions related to these systems. In line with studies implicating the right anterior insula in atypical switching between ECN and DMN in MDD, we expected to find a significant relation between boundary controllability and subclinical levels of depression in this region.

1. Methods

1.1. Participants

The sample was collected as part of a large research project (http://fcon_1000.projects.nitrc.org /indi/retro/southwestuni_qiu_index.html) exploring the associations among individual differences in brain structure and function, cognitive function, and mental health (Liu et al., 2017). Participants were recruited from Southwest University by means of the campus network, advertisements on bulletin boards and leaflets, or through face-to-face communications on campus. Before enrolling in the study, each participant was screened with a set of exclusion procedures involving self-reported questionnaires as well as structured and semi-structured interviews. All participants were required to be right-handed, and none had a history of psychiatric disorder, cognitive disability, substance abuse, or MRI contraindications.

In the current study, we only included participants that completed the Beck Depression Inventory (BDI, see below), which consisted of 351 participants. In addition, we excluded participants who had BDI scores with values higher than the cut-off score for severe clinical depression (BDI score of 30; Beck, Steer, & Carbin, 1988). Thus, the final sample included 349 participants (156 male, 191 female; average age of 20 years, $SD = 1.27$) with an average BDI score of 7 ($SD = 5.5$, skewness = .92). This research project was approved by the Southwest University Brain Imaging Center Institutional Review Board, and written informed consent was obtained from each participant. Participants received payment depending on time and tasks completed.

1.2. Materials

1.2.1. Behavioral measures

Depression Assessment—Depression was assessed using the BDI (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). The BDI is a 21-item self-report questionnaire measuring the severity of depressive symptoms within the past week. Participants who score higher in the BDI exhibit more depressive symptoms. The BDI is a reliable and widely used measure that assesses the severity of depressive symptoms from non-clinical to clinical samples (Beck, Steer, & Carbin, 1988).

1.2.2. MRI data acquisition

Imaging data were collected using a 12-channel head coil on a Siemens 3T Trio scanner (Siemens Medical Systems, Erlangen, Germany) at the Brain Imaging Center, Southwest University. High-resolution, three-dimensional T1-weighted structural images were obtained using a Magnetization Prepared Rapid Acquisition Gradient-echo sequence (TR/TE = 1,900 ms/2.52 ms, FA = 9°, resolution matrix = 256 × 256; slices = 176; thickness = 1.0 mm; voxel size = 1 × 1 × 1 mm^3). Diffusion tensor images were obtained using a diffusion-weighted, single shot, spin echo, EPI sequence (TR/TE = 11,000/98 ms, matrix = 128 × 128, field of view = 256 × 256 mm, voxel size = 2 × 2 × 2 mm^3, 60 axial slices, 2 mm slice thickness, b value 1 = 0 s/mm^2, b value 2 = 1,000 s/mm^2) in 30 directions and repeated acquisition of data three times to increase the signal-to-noise.

DTI data were reconstructed in DSI Studio (www.dsi-studio. labsolver.org) using q-space diffeomorphic reconstruction (QSDR; Yeh, Wedeen, & Tseng, 2011). QSDR first reconstructs diffusion-weighted images in native space and computes the quantitative anisotropy (QA) in each voxel. These QA values are used to warp the brain to a template QA volume in Montreal Neurological Institute (MNI) space using the statistical parametric mapping nonlinear registration algorithm. Once in MNI space, spin density functions were again reconstructed with a mean diffusion distance of 1.25 mm using three fiber orientations per voxel. Fiber tracking was performed in DSI Studio with an angular cut-off of 35, step size of 1.0 mm, minimum length of 10 mm, spin density function smoothing of 0, maximum length of 400 mm, and a QA threshold determined by its signal in the colony-stimulating factor. Deterministic fiber tracking using a modified FACT algorithm was performed until 1,000,000 streamlines were reconstructed for each individual. These parameters were chosen based on previous neurocognitive studies applying NCT (Betzel, Gu, Medaglia, Pasqualetti, & Bassett, 2016; Gu et al., 2015; Kenett et al., 2018; Medaglia et al., 2018a; Tang et al., 2017).

Anatomical scans were segmented using FreeSurfer (Fischl, 2012) and parcellated using the connectome mapping toolkit (Cammoun et al., 2012). Based on previous research (Gu et al., 2015; Hermundstad et al., 2013; Medaglia et al., 2016), a parcellation scheme including 234 brain regions (Cammoun et al., 2012) was registered to the B0 volume from each participant's DTI data. The B0 to MNI voxel mapping produced via QSDR was used to map region labels from native space to MNI coordinates. To extend region labels through the grey-white matter interface, the atlas was dilated by 4 mm (Cieslak & Grafton, 2014). Dilation was accomplished by filling non-labeled voxels with the statistical mode of their neighbors' labels. In the event of a tie, one of the modes was arbitrarily selected. Each streamline was labeled according to its terminal region pair. Finally, we conducted automatic quality control analysis to assess the quality of the DTI data (Roalf et al., 2016). For each participant's DTI data, we computed their temporal signal-to-noise ratio (tSNR). tSNR was computed by averaging each brain voxel's mean and standard deviation, after brain masking and motion correction. This analysis did not reveal any participants with an outlier tSNR values. As such, no participant was excluded based on this analysis.

From these data, we constructed structural connectivity networks that map streamline connections between 234 cortical and sub-cortical regions. In these anatomical connectivity matrices, brain regions are defined as nodes, and a link between two nodes represents the number of streamlines connecting them, normalized for their density (Sotiropoulos & Zalesky, 2017).

## 1.2.3. Network controllability analysis

To assess the ability of a certain brain region to influence other regions in different ways, we adopt the control theoretic notion of controllability. Controllability of a dynamical system refers to the possibility of driving the state of a dynamical system to a specific target state by means of an external control input (Tang & Bassett, 2018). Classic results in control theory ensure that controllability of the network is equivalent to the controllability Gramian matrix, which determines whether a linear system is controllable (Summers, Cortesi, & Lygeros, 2016). A rigorous mathematical formulation of network controllability in brain networks can be found in Gu et al. (2015). From the Gramian matrix, different controllability measures can be computed for each node (brain region) in the network. Here, based on previous research of network controllability in brain networks, we compute for each participant and each brain region their average controllability, modal controllability, and boundary controllability (Gu et al., 2015; Medaglia et al., 2016; Pasqualetti, Zampieri, & Bullo, 2014).

Average controllability identifies brain regions that, on average, can drive the system into different states with little effort (input energy). A state can be defined as the vector of neurophysiological activity magnitudes across brain regions at a single time point. Thus, regions with high average controllability can move the brain to many easily reachable states (Figure 1d). Thus, these regions may be important in allowing the brain to move smoothly between many cognitive functions that require little cognitive effort. Previous work has identified brain regions that demonstrate high average controllability, such as the precuneus, posterior cingulate, superior frontal, paracentral, precentral, and subcortical structures (Gu et al., 2015).

Modal controllability identifies brain regions that can drive the brain into different states that require high effort to achieve (those which require substantial input energy). Thus, regions with high modal controllability can move the brain to many difficult to reach states (Figure 1e). From a cognitive perspective, these regions may be important in switching the brain between functions that require significant cognitive effort. Previous work has identified brain regions that demonstrate high modal controllability, such as the postcentral, supramarginal, inferior parietal, pars orbitalis, medial orbitofrontal, and rostral middle frontal cortices (Gu et al., 2015).

Boundary controllability identifies brain regions that can drive the brain into states where different cognitive systems are either coupled or decoupled (Figure 1f). >From a cognitive perspective, these regions may be important in gating, synchronizing, or otherwise manipulating information across different cognitive processes. Previous work has identified brain regions that demonstrate high boundary controllability, such as the rostral middle frontal, lateral orbitofrontal, frontal pole, medial orbitofrontal, superior frontal, and anterior cingulate cortices (Gu et al., 2015).

Boundary controllability identifies network nodes that lie at the boundaries between network communities, as defined across all possible levels of hierarchical modularity in a network (Tang & Bassett, 2018). As such, an initial identification of brain modules (or communities) is required. While data-driven approaches have been developed to achieve such an identification, identifying brain modular organization remains an open challenge (see Medaglia et al., 2016). Here we chose to side step this issue and use a modular assignment that was computed via a data-driven approach that analyzed a large independent sample of resting
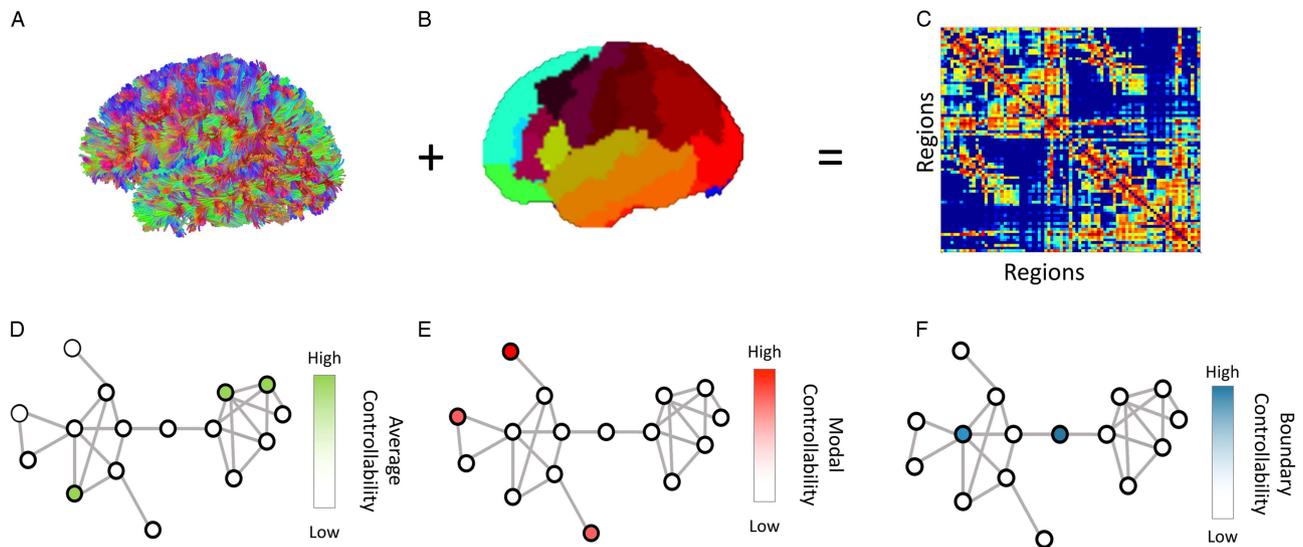
Figure 1. Overview of Methods: (A) We performed diffusion tractography for each participant, and (B) applied a probabilistic whole-brain parcellation. (C) anatomical connectivity matrices are constructed that represents the number of streamlines between pairs of regions, normalized by density. Finally, we define a simplified model of brain dynamics and simulate network control to quantify (D) average, (E) modal and (F) boundary controllability for each node (brain region) in the network for each participant. Figure adapted from Kenett et al. (2018).

state functional data using the same parcellation atlas. This approach, based on the method developed by Mišić et al. (2015), uses a consensus analysis to identify a partition that maximizes the modular partition of a large sample of independent datasets (Mišić et al., 2015). This partition identified 12 systems which are in line with neural systems identified in previous research (Dosenbach et al., 2010). Using this a priori independent modularity partition controls for the stochastic nature of the boundary controllability method and is justified by the identified relation between anatomical connectivity and resting state functional data (Honey et al., 2009).

1.2.4. Analysis overview

Our analysis process is as follows (Figure 1): We defined anatomical brain networks by subdividing the entire brain into 234 anatomically distinct brain regions (network nodes) in a commonly used anatomical atlas (Cammoun et al., 2012; Daducci et al., 2012; Hagmann et al., 2008). Following prior work (Bassett, Brown, Deshpande, Carlson, & Grafton, 2011; Gu et al., 2015; Hermundstad et al., 2013; Hermundstad et al., 2014), we connected nodes (brain regions) by the number of white matter streamlines identified by a commonly used deterministic tractography algorithm (Cieslak & Grafton, 2014). This procedure results in sparse, weighted, undirected structural brain networks for each participant. To control for volume confounds between pairs of brain regions i and j, streamline counts were normalized by dividing by the sum of streamlines brain region i has, which resulted in a measure of streamline density (Medaglia et al., 2016). Next, a simplified model of brain dynamics was applied to simulate network control and quantify average, modal, and boundary controllability for each brain region for each participant, as described above (Gu et al., 2015; Tang & Bassett, 2017). Intuitively, a node's average and modal controllability values are negatively related (Gu et al., 2015; Wu-Yan et al., 2018). This intuition was verified in a previous study analyzing the same dataset (Kenett et al., 2018).

We then conducted a whole-brain correlation analysis between BDI and each of the network controllability measures for all brain regions for all participants. As the BDI measure is skewed (skewness = .92), we conducted a Spearman rank correlation analysis for average, modal, and boundary controllability, controlling for multiple comparisons by calculating the false discovery rate (Benjamini & Hochberg, 1995; Benjamini & Yekutieli, 2001) with a false positive rate of 0.05. The brain networks were then visualized via the BrainNet Viewer (http://www.nitrc.org/projects/bnv/; Xia, Wang, & He, 2013). Anatomical labels were determined using the Brainnetome Atlas (http://atlas.brainnetome.org), which uses state-of-the-art multimodal neuroimaging techniques to provide a current fine-grained, cross-validated atlas and contains information on both anatomical and functional connections (Fan et al., 2016).

2. Results

We applied the network controllability analysis, as described above. To verify that the white matter connectivity matrices and controllability measures we compute are consistent with previous studies we conduct two initial inspections. First, we examine the consistency of our white matter connectivity matrices. To do so, we compare our white matter connectivity matrices to an external, published, data set of DTI data from 270 participants (Jung, Mead, Carrasco, & Flores, 2013). To compare the consistency of the white matter connectivity matrices in our sample, we conducted the following analysis: First, for each participant in each sample we computed Pearson's correlation across all pairs of vectors of their white matter connectivity matrices. Next, we computed the mean and standard deviation of the correlation matrix for each participant. Finally, we calculated the average over the average correlation distribution and the average over the standard deviation distribution for all participants in each sample. Since comparing across different DTI data sets is a challenge (Lebel, Treit, & Beaulieu, 2017), we only demonstrate that we achieve comparable results for the white matter consistency correlation distribution of our current data set (mean = 0.03, SD = 0.16) and this second sample (mean = 0.03, SD = 0.16).

Second, we examined whether our controllability measures computed over the sample map on to previously reported brain regions. To do so, we follow the approach conducted by Gu et al. (2015): We average the controllability scores for each brain region over all participants to derive a mean average, modal, and boundary score for each of our 234 brain regions. Next, for each controllability measure independently we examine the 30 brain regions with the highest scores for that controllability measure. In accordance with Gu et al. (2015), the top-30 average controllability brain regions included a majority of DMN regions such as the inferior parietal lobe and the medial frontal gyrus; the top-30 modal controllability brain regions included a majority of ECN regions such as the cingulo-operculum regions and also the insula; and the top-30 boundary controllability brain regions included a majority of attention regions including superior frontal areas and the frontal poles. Thus, our controllability analysis is consistent with previous reports on the dispersion of network controllability measures across the brain (Gu et al., 2015).

Next, we correlated the different network controllability measures across all brain regions with the BDI measure. This analysis revealed several brain regions that survived false discovery rate correction (Table 1; Figure 2), including a significant negative correlation with boundary controllability and BDI in the right anterior insula (adjusted $p < .001$). Furthermore, five regions exhibited a significant positive correlation with average controllability and a significant negative correlation with modal controllability: An area in the right inferior parietal lobe (IPL: average: adjusted $p < .001$; modal: adjusted $p < .001$), bilateral Lingual gyrus (right: average: adjusted $p < .001$; modal: adjusted $p < .001$; left: average: adjusted $p < .05$; modal: adjusted $p < .05$), and an area in the right lateral-occipital cortex (average: adjusted $p < .05$; modal: adjusted $p < .05$). A region within the left post-central gyrus also showed a negative correlation with average controllability and a positive correlation with modal controllability (average: adjusted $p < .05$; modal: adjusted $p < .05$).

3. Discussion

In the current study, we applied a novel computational approach— NCT —to quantify the relation between the role of different brain regions in theoretically "controlling" whole brain neural dynamics related to subclinical depressive symptoms. We argue that NCT can advance our understanding of evoked control processes related to subclinical levels of depression, as measured by the BDI. Our approach is motivated by previous initial work that has implicated the importance of average controllability in typical development and intelligence (Kenett et al., 2018; Tang et al., 2017) and modal and boundary controllability in cognitive control tasks and creativity (Kenett et al., 2018; Medaglia et al., 2016; Medaglia et al., 2018a). We conducted a NCT analysis on a large sample of par-

Table 1. Whole-brain correlation analysis between Beck Depression Inventory and network controllability measures (average, modal, and boundary) for the entire sample

Area	Hemisphere	BA	x	y	Z	Average	Boundary	Modal
Insula	Right	48	34	14	−6		− .20[***]	
Inferior parietal lobe	Right	39	42	−74	24	.13[*]		− .13[*]
Lingual	Right	17	10	−86	4	.14[*]		− .14[*]
Cuneus	Right	17	6	−86	26	.15[*]		− .15[*]
Fusiform	Right	37	32	−10	−36	.15[*]		− .15[*]
Post-central gyrus	Left	3	−42	−34	58	− .15[*]		.15[*]

Notes: Only correlations with brain regions that survived false discovery rate (FDR) are presented. All correlation values reported survived FDR correction; x, y, z coordinates represent the peak maximal voxel in Montreal Neurological Institute space. Anatomical labels were determined using the Brainnetome Atlas (BA) (http://atlas.brainnetome.org).
*$p < .05$; ***$p < .001$.
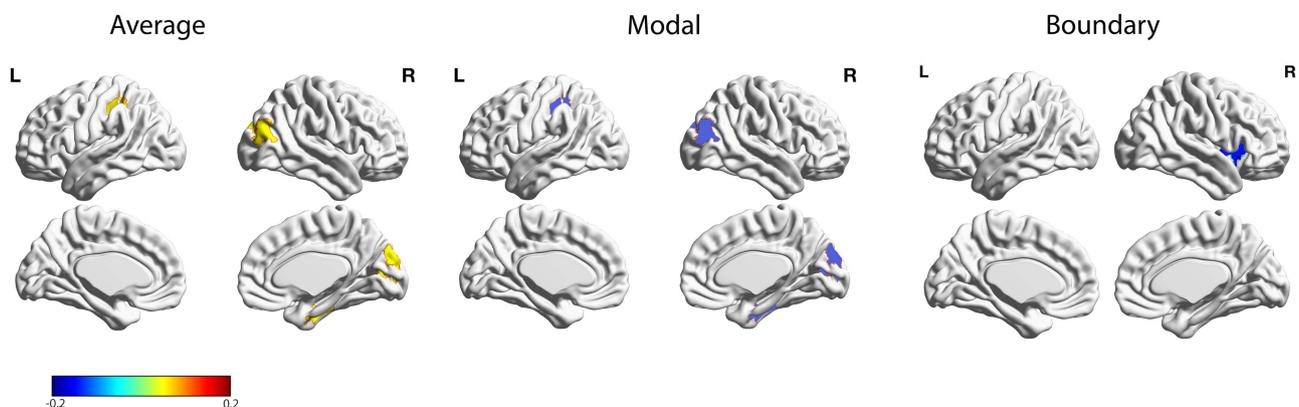
Figure 2. Relations between BDI and individual differences in average, modal, and boundary controllability anatomical brain networks. Maps highlight brain regions with significant correlation values that survived FDR correction. Warmer/colder colors indicate a positive/negative correlation between controllability and behavior.

ticipants ($N = 349$) who underwent diffusion tract imaging, alongside behavioral measurement of depressive symptoms. Our findings extend past work linking brain structure to subclinical depression by uncovering controllability effects within specific brain regions associated with depressive symptomology.

One main finding of the present study is a significant negative correlation between boundary controllability and BDI in the right anterior insula. The insula is part of the SN, which is implicated in coordinating behavioral responses through the detection and orientation toward internal and external stimuli (Menon, 2011; Seeley et al., 2007; Uddin, 2015). The right anterior insula is considered a key node in the SN, involved in mediating dynamics between the ECN and DMN (Uddin, 2015). Several studies have implicated this region in MDD (Diener et al., 2012; Hamilton, Furman et al., 2011; Iwabuchi et al., 2014; Manoliu et al., 2014; Strigo, Matthews, & Simmons, 2010; Wiebking et al., 2015). Manoliu et al. (2014) conducted a resting state functional connectivity analysis to investigate the relationship between the anterior insula dysfunction, altered brain network interaction, and severity of depression in MDD. The authors found that decreased functional connectivity of the right anterior insula within the SN was significantly correlated with the severity of MDD symptoms; such symptoms were also related to atypical functional connectivity between sub-systems of the ECN and DMN (Manoliu et al., 2014).

Manoliu et al. interpret their findings as supporting the hypothesis that dysfunction of the right anterior insula may be associated with abnormal interactions between ECN and DMN in patients with MDD. This abnormal interaction is a result of impaired right anterior insula-mediated control of network interaction (Menon, 2011). Previous studies have implicated the pivotal role of the right anterior insula in modulating interactions between the ECN and DMN (Sridharan, Levitin, & Menon, 2008), and clinical neuroscience has reported atypical activity and connectivity within these networks in patients with MDD (Hamilton, Furman et al., 2011). As such, the significant negative correlation between boundary controllability of the right anterior insula related to BDI reported in the present study strengthens and extends these previous findings. Importantly, NCT allows us to quantitatively characterize the role of the right anterior insula in mediating interactions between the ECN and DMN. Such a negative relation may be related to a diminished ability to integrate between ECN and DMN, which inhibits suppression of maladaptive and repetitive thought, linked to hyper activity in the DMN (Hamilton, Furman et al., 2011).

We also found a significant positive relation between BDI and average controllability in several right hemisphere brain regions, including the IPL, lingual gyrus, fusiform, and cuneus. While still debated, a few studies have found atypical activation in the right IPL related to depression (Hao et al., 2015; Li, et al., 2015; Sheline et al., 2009). Based on the role of the right IPL in attentional processing of emotional stimuli (Canli et al., 2004), Hao et al. (2015) found that depressed patients exhibited higher IPL activation when processing sad emotional stimuli. Li et al. (2015) found decreased grey matter volume in a sample of women with subclinical depression. The authors interpreted this finding as indicating that reduced IPL volume may induce inefficient attentional control on negative emotion processing (Li et al., 2015). While the bilateral lingual gyrus and the lateral occipital gyrus areas are less commonly related to depression, a few studies have revealed abnormal activation in these areas (Jung et al., 2014; Keedwell et al., 2009; Veer et al., 2010). Keedwell et al. (2009)

demonstrated an emotional processing bias towards negative information in the lingual gyrus and the primary visual cortex, and Veer et al. (2010) found decreased functional connectivity of the bilateral lingual gyrus in MDD. In the context of the present study, we suspect that subclinical depressive symptoms may be related to deficits in controlling visual-affective information flow, as related to higher average controllability in these areas.

Finally, we found a weak significant positive correlation between modal controllability and depression in the post-central gyrus. Although the postcentral gyrus has been linked to modal controllability in non-clinical samples (Gu et al., 2015), to our knowledge, this is the first study linking structural and functional deficits in this region to depressive symptomology . Future work should replicate and further examine how controllability within the postcentral gyrus relates to subclinical and clinical depressive symptoms.

The current study adds to a growing amount of studies that have demonstrated the strength of applying NCT to study neural dynamics related to different cognitive phenomena (Kenett et al., 2018; Medaglia et al., 2016; Medaglia et al., 2018a; Tang et al., 2017). In relation to clinical population, to the best of our knowledge, only one study similar to ours exist (Jeganathan et al., 2018). Jeganathan et al. (2018) investigated average controllability and network characteristics of white matter connectivity networks in participants with bipolar depression, participants with high risk of bipolar depression, and controls. The authors found average controllability deficits (lower compared with controls) in a left lateralized network of brain regions that included the inferior frontal gyrus, insula, and the postcentral gyrus in participants with bipolar depression. The authors also found average controllability deficits in a right lateralized network of brain regions that included the prefrontal cortex and striatal regions in participants with high risk of bipolar depression. The authors interpret their findings regarding the altered average controllability in participants with bipolar depression as related to altered connectivity between these regions, mediating dysfunctional cognition with emotional homeostasis (Jeganathan et al., 2018). It is important to note that while our study is related to the work of Jeganathan et al. (2018), we examined a sample of participants with subclinical levels of depression and examined a broader range of controllability measures. Regardless, the work of Jeganathan et al. (2018) and the current study demonstrate how such a quantitative approach can be applied to study psychopathology such as MDD and bipolar depression. Further research is needed to quantify the spectrum of varying degrees of depression and the neural dynamics leading to these varying states.

The focus of the current study is on atypical inhibition and rumination as signals of maladaptive cognitive control related to depression and how NCT can be applied to quantify such signals. However, it is important to note that the BDI measures both a psychological–cognitive factor and an affective–somatic factor (Steer, Ball, Ranieri, & Beck, 1999; Storch, Robert, & Roth, 2004). While rumination is attributed to hyper-connectivity in the DMN (Hamilton, Furman et al., 2011), Burrows, Timpano, and Uddin (2017) have recently proposed that rumination is related to dysfunction in the SN, specifically the insula (Burrows, Timpano, & Uddin, 2017). This hypothesis is supported by atypical connectivity patterns between the SN and DMN related to rumination (Kaiser et al., 2016), and also to recent findings that altered insula timing in coupling between ECN and DMN is altered in patients with MDD (Hamilton, Furman et al., 2011). Burrows,

Timpano, and Uddin (2017) interpret this atypical timing of the anterior insula as potentially indicating processing of heightened salience of negative information in participants with MDD. Our main finding of a negative correlation between boundary controllability in the anterior insula and BDI supports the hypothesis on the role of the SN in rumination and offers a potential bridge across the two factors measured by the BDI.

A few limitations in our study exist. First, the controllability metrics are calculated over the entire space of all possible states. In reality, however, neural systems occupy a restricted space of biologically viable configurations, generally avoiding pathological states (e.g., seizures) and states that require too much energy to reach. While methods for controlling transitions between specific configurations in a restricted state space are beginning to be explored (Betzel et al., 2016; Gu et al., 2017), those methods are not yet fully developed and require the researcher to specify states of interest. For this reason, the focus of the present analysis was on the behavior relevance of average, modal, and boundary controllability, which do not require such researcher input.

A second limitation is in the method we used to measure structural connectivity, which was based on DTI data. DTI may under-sample some white matter fibers, particularly those linking hemispheres or those that cross paths with other fibers (Wedeen et al., 2008). This can also partially account for the weak correlations, albeit significant, found in our data. Future efforts should apply diffusion spectrum imaging to improve estimates of structural network architecture.

Third, our boundary controllability analysis was based on an independent a priori brain modularity partition, which was in turn based on a modularity analysis of resting-state functional imaging data (Mišić et al., 2015). This partition was chosen as an objective initial template for the analysis and also based on the relation between structural connectivity networks and resting-state data (Cole et al., 2016; Hermundstad et al., 2014). However, the partition we chose may partially bias our results. Future research is needed to establish independent a priori partitions based on structural networks, which will increase the reliability and validity of the boundary controllability analysis.

Finally, recently the ability of specific nodes in a network (such as anatomical brain networks) to drive the system into a specific state has been questioned (Menara, Gu, Bassett, & Pasqualetti, 2017; Tu et al., 2018). In the current study, we were interested in investigating the theoretical notion of NCT and individual differences in depressive symptoms, without committing to linking between cognitive control processes and network controllability.

In conclusion, while rumination and atypical inhibition are considered indicators of atypical cognitive control process in depression, they are far from understood. We propose a method to computationally quantify the role of different brain regions in theoretically "controlling" the brain as related to subclinical levels of depression symptoms. Our results provide unique and novel evidence on how individual differences in controllability measures across the brain correlate with behavioral measures of depression symptoms. Thus, our results demonstrate the feasibility of applying NCT to advance our understanding of different drivers of neural dynamics relate to subclinical levels of depression.

Conflict of Interest. The authors declare no conflicts of interest.

References

Abdelnour, F., Voss, H. U., & Raj, A. (2014). Network diffusion accurately models the relationship between structural and functional brain connectivity networks. *Neuroimage*, 90, 335–347. https://doi.org/10.1016/j.neuroimage.2013.12.039

Andrews-Hanna, J. R., Smallwood, J., & Spreng, R. N. (2014). The default network and self-generated thought: Component processes, dynamic control, and clinical relevance. *Annals of the New York Academy of Sciences*, 1316, 29–52. http://dx.doi.org/10.1111/nyas.12360

Bai, F., Shu, N., Yuan, Y., Shi, Y., Yu, H., Wu, D., … Zhang, Z. (2012). Topologically convergent and divergent structural connectivity patterns between patients with remitted geriatric depression and amnestic mild cognitive impairment. *Journal of Neuroscience*, 32, 4307–4318. https://doi.org/10.1523/JNEUROSCI.5061-11.2012

Bassett, D. S., Brown, J. A., Deshpande, V., Carlson, J. M., & Grafton, S. T. (2011). Conserved and variable architecture of human white matter connectivity. *Neuroimage*, 54, 1262–1279. http://dx.doi.org/10.1016/j.neuroimage.2010.09.006

Beck, A. T. (1976). *Cognitive therapy and the emotional disorders*. New York, NY: International University Press.

Beck, A. T., Steer, R. A., & Carbin, M. G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review*, 8, 77–100. https://doi.org/10.1016/0272-7358(88)90050-5

Beck, A. T., Ward, C. H., Mendelson, M. M., Mock, J. J., & Erbaugh, J. J. (1961). An inventory for measuring depression. *Archives of General Psychiatry*, 4, 561–571. http://dx.doi.org/10.1001/archpsyc.1961.01710120031004

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society. Series B*, 57, 289–300.

Benjamini, Y., & Yekutieli, D. (2001). The control of the false discovery rate in multiple testing under dependency. *Annals of Statistics*, 29, 1165–1188. https://doi.org/10.1214/aos/1013699998

Bettinardi, R. G., Deco, G., Karlaftis, V. M., Van Hartevelt, T. J., Fernandes, H. M., Kourtzi, Z., … Zamora-López, G. (2017). How structure sculpts function: Unveiling the contribution of anatomical connectivity to the brain's spontaneous correlation structure. *Chaos: An Interdisciplinary Journal of Nonlinear Science*, 27, 047409. http://dx.doi.org/10.1063/1.4980099

Betzel, R. F., Gu, S., Medaglia, J. D., Pasqualetti, F., & Bassett, D. S. (2016). Optimally controlling the human connectome: The role of network topology. *Scientific Reports*, 6, 30770. http://dx.doi.org/10.1038/srep30770

Burrows, C. A., Timpano, K. R., & Uddin, L. Q. (2017). Putative brain networks underlying repetitive negative thinking and comorbid internalizing problems in autism. *Clinical Psychological Science*, 5, 522–536. http://dx.doi.org/10.1177/2167702616683506

Calhoon, G. G., & Tye, K. M. (2015). Resolving the neural circuits of anxiety. *Nature Neuroscience*, 18, 1394–1404. http://dx.doi.org/10.1038/nn.4101

Cammoun, L., Gigandet, X., Meskaldji, D., Thiran, J. P., Sporns, O., Do, K. Q., … Hagmann, P. (2012). Mapping the human connectome at multiple scales with diffusion spectrum MRI. *Journal of Neuroscience Methods*, 203, 386–397. http://dx.doi.org/10.1016/j.jneumeth.2011.09.031

Canli, T., Sivers, H., Thomason, M. E., Whitfield-Gabrieli, S., Gabrieli, J. D. E., & Gotlib, I. H. (2004). Brain activation to emotional words in depressed vs healthy subjects. *NeuroReport*, 15, 2585–2588.

Choi, K. S., Holtzheimer, P. E., Franco, A. R., Kelley, M. E., Dunlop, B. W., Hu, X. P., & Mayberg, H. S. (2014). Reconciling variable findings of white matter integrity in major depressive disorder. *Neuropsychopharmacology*, 39, 1332–1339. http://dx.doi.org/10.1038/npp.2013.345

Cieslak, M., & Grafton, S. T. (2014). Local termination pattern analysis: A tool for comparing white matter morphology. *Brain Imaging and Behavior*, 8, 292–299. http://dx.doi.org/10.1007/s11682-013-9254-z

Cole, M. W., Ito, T., Bassett, D. S., & Schultz, D. H. (2016). Activity flow over resting-state networks shapes cognitive task activations. *Nature Neuroscience*, 19, 1718–1726. http://dx.doi.org/10.1038/nn.4406

Cole, M. W., Repovš, G., & Anticevic, A. (2014). The frontoparietal control system: A central role in mental health. *The Neuroscientist*, 20, 652–664. http://dx.doi.org/10.1177/1073858414525995

Cooney, R. E., Joormann, J., Eugène, F., Dennis, E. L., & Gotlib, I. H. (2010). Neural correlates of rumination in depression. *Cognitive, Affective, & Behavioral Neuroscience*, 10, 470–478. http://dx.doi.org/10.3758/CABN.10.4.470

Daducci, A., Gerhard, S., Griffa, A., Lemkaddem, A., Cammoun, L., Gigandet, X., … Thiran, J.-P. (2012). The connectome mapper: An open-source processing pipeline to map connectomes with MRI. *PLoS One*, 7, e48121. http://dx.doi.org/10.1371/journal.pone.0048121

De Witte, N. A. J., & Mueller, S. C. (2017). White matter integrity in brain networks relevant to anxiety and depression: Evidence from the human connectome project dataset. *Brain Imaging and Behavior*, 11, 1604–1615. http://dx.doi.org/10.1007/s11682-016-9642-2

Diener, C., Kuehner, C., Brusniak, W., Ubl, B., Wessa, M., & Flor, H. (2012). A meta-analysis of neurofunctional imaging studies of emotion and cognition in major depression. *Neuroimage*, 61, 677–685. https://doi.org/10.1016/j.neuroimage.2012.04.005

Dosenbach, N. U. F., Nardos, B., Cohen, A. L., Fair, D. A., Power, J. D., Church, J. A., … Lessov-Schlaggar, C. N. (2010). Prediction of individual brain maturity using fMRI. *Science*, 329, 1358–1361. http://dx.doi.org/10.1126/science.1194144

Fan, L., Li, H., Zhuo, J., Zhang, Y., Wang, J., Chen, L., … Jiang, T. (2016). The human brainnetome atlas: A new brain atlas based on connectional architecture. *Cerebral Cortex*, 26, 3508–3526. http://dx.doi.org/10.1093/cercor/bhw157

Fischl, B. (2012). FreeSurfer. *Neuroimage*, 62, 774–781. https://doi.org/10.1016/j.neuroimage.2012.01.021

Galán, R. F. (2008). On how network architecture determines the dominant patterns of spontaneous neural activity. *PLoS One*, 3, e2148. https://doi.org/10.1371/journal.pone.0002148

Gong, Q., & He, Y. (2015). Depression, neuroimaging and connectomics: A selective overview. *Biological Psychiatry*, 77, 223–235. https://doi.org/10.1016/j.biopsych.2014.08.009

Griffa, A., Baumann, P. S., Thiran, J.-P., & Hagmann, P. (2013). Structural connectomics in brain diseases. *NeuroImage*, 80, 515–526. https://doi.org/10.1016/j.neuroimage.2013.04.056

Gu, S., Betzel, R. F., Mattar, M. G., Cieslak, M., Delio, P. R., Grafton, S. T., … Bassett, D. S. (2017). Optimal trajectories of brain state transitions. *NeuroImage*, 148, 305–317. https://doi.org/10.1016/j.neuroimage.2017.01.003

Gu, S., Pasqualetti, F., Cieslak, M., Telesford, Q. K., Yu, A. B., Kahn, A. E., … Bassett, D. S. (2015). Controllability of structural brain networks. *Nature Communications*, 6, 1–10. http://dx.doi.org/10.1038/ncomms9414

Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C. J., Wedeen, V. J., & Sporns, O. (2008). Mapping the structural core of human cerebral cortex. *PLoS Biology*, 6, e159. http://dx.doi.org/10.1371/journal.pbio.0060159

Hamilton, J. P., Chen, G., Thomason, M. E., Schwartz, M. E., & Gotlib, I. H. (2011). Investigating neural primacy in major depressive disorder: Multivariate Granger causality analysis of resting-state fMRI time-series data. *Molecular Psychiatry*, 16, 763–772. http://dx.doi.org/10.1038/mp.2010.46

Hamilton, J. P., Chen, M. C., & Gotlib, I. H. (2013). Neural systems approaches to understanding major depressive disorder: An intrinsic functional organization perspective. *Neurobiology of Disease*, 52, 4–11. http://dx.doi.org/10.1016/j.nbd.2012.01.015

Hamilton, J. P., Furman, D. J., Chang, C., Thomason, M. E., Dennis, E., & Gotlib, I. H. (2011). Default-mode and task-positive network activity in major depressive disorder: Implications for adaptive and maladaptive rumination. *Biological Psychiatry*, 70, 327–333. http://dx.doi.org/10.1016/j.biopsych.2011.02.003

Hamilton, J. P., Glover, G. H., Bagarinao, E., Chang, C., Mackey, S., Sacchet, M. D., & Gotlib, I. H. (2016). Effects of salience-network-node neurofeedback training on affective biases in major depressive disorder. *Psychiatry Research: Neuroimaging*, 249, 91–96. http://dx.doi.org/10.1016/j.pscychresns.2016.01.016

Hao, L., Yang, J., Wang, Y., Zhang, S., Xie, P., Luo, Q., … Qiu, J. (2015). Neural correlates of causal attribution in negative events of depressed patients: Evidence from an fMRI study. *Clinical Neurophysiology*, 126, 1331–1337. https://doi.org/10.1016/j.clinph.2014.10.146

Hermundstad, A. M., Bassett, D. S., Brown, K. S., Aminoff, E. M., Clewett, D., Freeman, S., … Miller, M. B. (2013). Structural foundations of resting-state and task-based functional connectivity in the human brain. *Proceedings of the National Academy of Sciences*, 110, 6169–6174. http://dx.doi.org/10.1073/pnas.1219562110

Hermundstad, A. M., Brown, K. S., Bassett, D. S., Aminoff, E. M., Frithsen, A., Johnson, A., … Carlson, J. M. (2014). Structurally-constrained relationships between cognitive states in the human brain. *PLoS Computational Biology*, 10, e1003591. https://doi.org/10.1371/journal.pcbi.1003591

Honey, C. J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J.-P., Meuli, R. Hagmann, P. (2009). Predicting human resting-state functional connectivity from structural connectivity. *Proceedings of the National Academy of Sciences*, 106, 2035–2040. http://dx.doi.org/10.1073/pnas.0811168106

Honey, C. J., Thivierge, J.-P., & Sporns, O. (2010). Can structure predict function in the human brain? *Neuroimage*, 52, 766–776. https://doi.org/10.1016/j.neuroimage.2010.01.071

Iwabuchi, S. J., Peng, D., Fang, Y., Jiang, K., Liddle, E. B., Liddle, P. F., & Palaniyappan, L. (2014). Alterations in effective connectivity anchored on the insula in major depressive disorder. *European Neuropsychopharmacology*, 24, 1784–1792. http://dx.doi.org/10.1016/j.euroneuro.2014.08.005

Jeganathan, J., Perry, A., Bassett, D. S., Roberts, G., Mitchell, P. B., & Breakspear, M. (2018). Fronto-limbic dysconnectivity leads to impaired brain network controllability in young people with bipolar disorder and those at high genetic risk. *NeuroImage: Clinical*, 19, 71–81. http://dx.doi.org/10.1016/j.nicl.2018.03.032.

Jung, J. Y., Kang, J., Won, E., Nam, K., Lee, M.-S., Tae, W. S., & Ham, B.-J. (2014). Impact of lingual gyrus volume on antidepressant response and neurocognitive functions in major depressive disorder: A voxel-based morphometry study. *Journal of Affective Disorders*, 169, 179–187. http://dx.doi.org/10.1016/j.jad.2014.08.018

Jung, R. E., Mead, B. S., Carrasco, J., & Flores, R. A. (2013). The structure of creative cognition in the human brain. *Frontiers in Human Neuroscience*, 7, 330. http://dx.doi.org/10.3389/fnhum.2013.00330

Kaiser, R. H., Whitfield-Gabrieli, S., Dillon, D. G., Goer, F., Beltzer, M., Minkel, J., … Pizzagalli, D. A. (2016). Dynamic resting-state functional connectivity in major depression. *Neuropsychopharmacology*, 41, 1822–1830. http://dx.doi.org/10.1038/npp.2015.352

Keedwell, P., Drapier, D., Surguladze, S., Giampietro, V., Brammer, M., & Phillips, M. (2009). Neural markers of symptomatic improvement during antidepressant therapy in severe depression: Subgenual cingulate and visual cortical responses to sad, but not happy, facial stimuli are correlated with changes in symptom score. *Journal of Psychopharmacology*, 23, 775–788. http://dx.doi.org/10.1177/0269881108093589

Kenett, Y. N., Medaglia, J. D., Beaty, R. E., Chen, Q., Betzel, R. F., Thompson-Schill, S. L., & Qiu, J. (2018). Driving the brain towards creativity and intelligence: A network control theory analysis. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2018.01.001

Korgaonkar, M. S., Fornito, A., Williams, L. M., & Grieve, S. M. (2014). Abnormal structural networks characterize major depressive disorder: A connectome analysis. *Biological Psychiatry*, 76, 567–574. http://dx.doi.org/10.1016/j.biopsych.2014.02.018

Lebel, C., Treit, S., & Beaulieu, C. (2017). A review of diffusion MRI of typical white matter development from early childhood to young adulthood. *NMR in Biomedicine*, e3778. http://dx.doi.org/10.1002/nbm.3778

Li, H., Wei, D., Sun, J., Chen, Q., Zhang, Q., & Qiu, J. (2015). Brain structural alterations associated with young women with subthreshold depression. *Scientific Reports*, 5, 9707. http://dx.doi.org/10.1038/srep09707

Liu, W., Wei, D., Chen, Q., Yang, W., Meng, J., Wu, G., … Qiu, J. (2017). Longitudinal test-retest neuroimaging data from healthy young adults in southwest China. *Scientific Data*, 4, 170017. http://dx.doi.org/10.1038/sdata.2017.17

Liu, Y.-Y., Slotine, J.-J., & Barabási, A.-L. (2011). Controllability of complex networks. *Nature*, 473, 167–173. http://dx.doi.org/10.1038/nature10011

Liu, Z., Xu, C., Xu, Y., Wang, Y., Zhao, B., Lv, Y., … Du, C. (2010). Decreased regional homogeneity in insula and cerebellum: A resting-state fMRI study in patients with major depression and subjects at high risk for

major depression. *Psychiatry Research: Neuroimaging*, *182*, 211–215. https://doi.org/10.1016/j.pscychresns.2010.03.004

Manoliu, A., Meng, C., Brandl, F., Doll, A., Tahmasian, M., Scherr, M., … Sorg, C. (2014). Insular dysfunction within the salience network is associated with severity of symptoms and aberrant inter-network connectivity in major depressive disorder. *Frontiers in Human Neuroscience*, *7*, 930. http://dx.doi.org/10.3389/fnhum.2013.00930

Medaglia, J. D., Gu, S., Pasqualetti, F., Ashare, R. L., Lerman, C., Kable, J., & Bassett, D. S. (2016). Cognitive control in the controllable connectome. *arXiv preprint*.

Medaglia, J. D., Harvey, D. Y., White, N., Kelkar, A., Zimmerman, J., Bassett, D. S., & Hamilton, R. H. (2018a). Network controllability in the inferior frontal gyrus relates to controlled language variability and susceptibility to TMS. *The Journal of Neuroscience, 38*, 6399–6410. http://dx.doi.org/10.1523/jneurosci.0092-17.2018.

Medaglia, J. D., Huang, W., Karuza, E. A., Kelkar, A., Thompson-Schill, S. L., Ribeiro, A., & Bassett, D. S. (2018b). Functional alignment with anatomical networks is associated with cognitive flexibility. *Nature Human Behaviour, 2*, 156–164. http://dx.doi.org/10.1038/s41562-017-0260-9

Menara, T., Gu, S., Bassett, D. S., & Pasqualetti, F. (2017). On structural controllability of symmetric (brain) networks. *arXiv preprint*.

Menon, V. (2011). Large-scale brain networks and psychopathology: A unifying triple network model. *Trends in Cognitive Sciences*, *15*, 483–506. http://dx.doi.org/10.1016/j.tics.2011.08.003

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: A network model of insula function. *Brain Structure and Function*, *214*, 655–667. https://doi.org/10.1007/s00429-010-0262-0

Mišić, B., Betzel, R. F., Nematzadeh, A., Goñi, J., Griffa, A., Hagmann, P., … Sporns, O. (2015). Cooperative and competitive spreading dynamics on the human connectome. *Neuron*, *86*, 1518–1529. http://dx.doi.org/10.1016/j.neuron.2015.05.035

Muldoon, S. F., Pasqualetti, F., Gu, S., Cieslak, M., Grafton, S. T., Vettel, J. M., & Bassett, D. S. (2016). Stimulation-based control of dynamic brain networks. *PLoS Computational Biology*, *12*, e1005076. http://dx.doi.org/10.1371/journal.pcbi.1005076

Murphy, M. L., & Frodl, T. (2011). Meta-analysis of diffusion tensor imaging studies shows altered fractional anisotropy occurring in distinct brain areas in association with depression. *Biology of Mood & Anxiety Disorders*, *1*, 3. https://doi.org/10.1186/2045-5380-1-3

Nolen-Hoeksema, S., & Morrow, J. (1993). Effects of rumination and distraction on naturally occurring depressed mood. *Cognition & Emotion*, *7*, 561–570. https://doi.org/10.1080/02699939308409206

Pasqualetti, F., Zampieri, S., & Bullo, F. (2014). Controllability metrics, limitations and algorithms for complex networks. *IEEE Transactions on Control of Network Systems*, *1*, 40–52. https://doi.org/10.1109/TCNS.2014.2310254

Qin, J., Wei, M., Liu, H., Yan, R., Luo, G., Yao, Z., & Lu, Q. (2014). Abnormal brain anatomical topological organization of the cognitive-emotional and the frontoparietal circuitry in major depressive disorder. *Magnetic Resonance in Medicine*, *72*, 1397–1407. http://dx.doi.org/10.1002/mrm.25036

Rizk, M. M., Rubin-Falcone, H., Keilp, J., Miller, J. M., Sublette, M. E., Burke, A., … Mann, J. J. (2017). White matter correlates of impaired attention control in major depressive disorder and healthy volunteers. *Journal of Affective Disorders*, *222*, 103–111. http://dx.doi.org/10.1016/j.jad.2017.06.066

Roalf, D. R., Quarmley, M., Elliott, M. A., Satterthwaite, T. D., Vandekar, S. N., Ruparel, K., … Gur, R. E. (2016). The impact of quality assurance assessment on diffusion tensor imaging outcomes in a large-scale population-based cohort. *NeuroImage*, *125*, 903–919. https://doi.org/10.1016/j.neuroimage.2015.10.068

Schultz, D. H., Ito, T., Solomyak, L. I., Chen, R. H., Mill, R. D., Anticevic, A., & Cole, M. W. (2018). Global connectivity of the frontoparietal cognitive control network is related to depression symptoms in the general population. *Network Neuroscience*, posted online April 12, 2018. https://doi.org/10.1162/netn_a_00056

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., … Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of*

Neuroscience, *27*, 2349–2356. http://dx.doi.org/10.1523/JNEUROSCI.5587-06.2007

Sexton, C. E., Mackay, C. E., & Ebmeier, K. P. (2009). A systematic review of diffusion tensor imaging studies in affective disorders. *Biological Psychiatry*, *66*, 814–823. https://doi.org/10.1016/j.biopsych.2009.05.024

Sheline, Y. I., Barch, D. M., Price, J. L., Rundle, M. M., Vaishnavi, S. N., Snyder, A. Z., … Raichle, M. E. (2009). The default mode network and self-referential processes in depression. *Proceedings of the National Academy of Sciences*, *106*, 1942–1947. http://dx.doi.org/10.1073/pnas.0812686106

Sotiropoulos, S. N., & Zalesky, A. (2017). Building connectomes using diffusion MRI: Why, how and but. *NMR in Biomedicine*, *e3752*, 1–23. http://doi.org/10.1002/nbm.3752

Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the National Academy of Sciences*, *105*, 12569–12574. https://doi.org/10.1073/pnas.0800005105

Steer, R. A., Ball, R., Ranieri, W. F., & Beck, A. T. (1999). Dimensions of the Beck depression inventory-II in clinically depressed outpatients. *Journal of Clinical Psychology*, *55*, 117–128. https://doi.org/10.1002/(SICI)1097-4679 (199901)55:1<117::AID-JCLP12>3.0.CO;2-A

Storch, E. A., Robert, J. W., & Roth, D. A. (2004). Factor structure, concurrent validity, and internal consistency of the beck depression inventory—second edition in a sample of college students. *Depression and Anxiety*, *19*, 187–189. http://dx.doi.org/10.1002/da.20002

Strigo, I. A., Matthews, S. C., & Simmons, A. N. (2010). Right anterior insula hypoactivity during anticipation of homeostatic shifts in major depressive disorder. *Psychosomatic Medicine*, *72*, 316–323. http://dx.doi.org/10.1097/PSY.0b013e3181d07873

Summers, T. H., Cortesi, F. L., & Lygeros, J. (2016). On submodularity and controllability in complex dynamical networks. *IEEE Transactions on Control of Network Systems*, *3*, 91–101. http://dx.doi.org/10.1109/TCNS.2015.2453711

Tang, E., & Bassett, D. S. (2018). Colloquium: Control of dynamics in brain networks. *Reviews of Modern Physics, 90*, 031003. http://dx.doi.org/10.1103/RevModPhys.90.031003

Tang, E., Giusti, C., Baum, G. L., Gu, S., Pollock, E., Kahn, A. E., … Bassett, D. S. (2017). Developmental increases in white matter network controllability support a growing diversity of brain dynamics. *Nature Communications*, *8*, 1252. http://dx.doi.org/10.1038/s41467-017-01254-4

Tu, C., Rocha, R. P., Corbetta, M., Zampieri, S., Zorzi, M., & Suweis, S. (2018). Warnings and caveats in brain controllability. *NeuroImage, 176*, 83–91. https://doi.org/10.1016/j.neuroimage.2018.04.010

Uddin, L. Q. (2015). Salience processing and insular cortical function and dysfunction. *Nature Reviews Neuroscience*, *16*, 55–61. http://dx.doi.org/10.1038/nrn3857

Veer, I. M., Beckmann, C. F., Van Tol, M.-J., Ferrarini, L., Milles, J., Veltman, D. J., … Rombouts, S. A. (2010). Whole brain resting-state analysis reveals decreased functional connectivity in major depression. *Frontiers in Systems Neuroscience*, *4*, 41. http://dx.doi.org/10.3389/fnsys.2010.00041.

Wedeen, V. J., Wang, R. P., Schmahmann, J. D., Benner, T., Tseng, W. Y. I., Dai, G., … de Crespigny, A. J. (2008). Diffusion spectrum magnetic resonance imaging (DSI) tractography of crossing fibers. *Neuroimage*, *41*, 1267–1277. http://dx.doi.org/10.1016/j.neuroimage.2008.03.036

White, T., Nelson, M., & Lim, K. O. (2008). Diffusion tensor imaging in psychiatric disorders. *Topics in Magnetic Resonance Imaging*, *19*, 97–109. http://dx.doi.org/10.1097/RMR.0b013e3181809f1e

Wiebking, C., de Greck, M., Duncan, N. W., Tempelmann, C., Bajbouj, M., & Northoff, G. (2015). Interoception in insula subregions as a possible state marker for depression—an exploratory fMRI study investigating healthy, depressed and remitted participants. *Frontiers in Behavioral Neuroscience*, *9*, 82. https://doi.org/10.3389/fnbeh.2015.00082

Wu-Yan, E., Betzel, R. F., Tang, E., Gu, S., Pasqualetti, F., & Bassett, D. S. (2018). Benchmarking measures of network controllability on canonical graph models. *Journal of Nonlinear Science*. http://dx.doi.org/10.1007/s00332-018-9448-z

Xia, M., Wang, J., & He, Y. (2013). BrainNet viewer: A network visualization tool for human brain connectomics. *PLoS One*, *8*, e68910. http://dx.doi.org/10.1371/journal.pone.0068910

Yan, G., Vértes, P. E., Towlson, E. K., Chew, Y. L., Walker, D. S., Schafer, W. R., & Barabási, A.-L. (2017). Network control principles predict neuron function in the Caenorhabditis elegans connectome. *Nature*, *550*, 519–523. http://dx.doi.org/10.1038/nature24056

Yeh, F.-C., Wedeen, V. J., & Tseng, W.-Y. I. (2011). Estimation of fiber orientation and spin density distribution by diffusion deconvolution. *Neuroimage*, *55*, 1054–1062. http://dx.doi.org/10.1016/j.neuroimage.2010.11.087

Zabelina, D. L., & Andrews-Hanna, J. R. (2016). Dynamic network interactions supporting internally-oriented cognition. *Current opinion in Neurobiology*, *40*, 86–93. http://dx.doi.org/10.1016/j.conb.2016.06.014