Disrupted Effective Connectivity of Cortical Systems Supporting Attention and Interoception in Melancholia

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IMPORTANCE Patients with melancholia report a distinct and intrusive dysphoric state during internally generated thought. Melancholia has long been considered to have a strong biological component, but evidence for its specific neurobiological origins is limited. The distinct neurocognitive, psychomotor, and mood disturbances observed in melancholia do, however, suggest aberrant coordination of frontal-subcortical circuitry, which may best be captured through analysis of complex brain networks.

OBJECTIVE To investigate the effective connectivity between spontaneous (resting-state) brain networks in melancholia, focusing on networks underlying attention and interoception.

DESIGN, SETTING, AND PARTICIPANTS We performed a cross-sectional, observational, resting-state functional magnetic resonance imaging study of 16 participants with melancholia, 16 with nonmelancholic depression, and 16 individuals serving as controls at a hospital-based research institute between August 30, 2010, and June 27, 2012. We identified 5 canonical resting-state networks (default mode, executive control, left and right frontoparietal attention, and bilateral anterior insula) and inferred spontaneous interactions among these networks using dynamic causal modeling.

MAIN OUTCOMES AND MEASURES Graph theoretic measures of brain connectivity, namely, in-degree and out-degree of each network and edge connectivity, between regions composed our principal between-group contrasts.

RESULTS Melancholia was characterized by a pervasive disconnection involving anterior insula and attentional networks compared with participants in the control (Mann-Whitney, 189.00; z = 2.38; P = .02) and nonmelancholic depressive (Mann-Whitney, 203.00; z = 2.93; P = .004) groups. Decreased effective connectivity between the right frontoparietal and insula networks was present in participants with melancholic depression compared with those with nonmelancholic depression (χ² = 8.13; P = .004). Reduced effective connectivity between the insula and executive networks was found in individuals with melancholia compared with healthy controls (χ² = 8.96; P = .003).

CONCLUSIONS AND RELEVANCE We observed reduced effective connectivity in resting-state functional magnetic resonance imaging between key networks involved in attention and interoception in melancholia. We propose that these abnormalities underlie the impoverished variety and affective quality of internally generated thought in this disorder.

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Disrupt ed Effective Connectivity in Melancholia

Despite advances in pursuing the neurobiological causes of clinical depressive conditions, the literature is characterized by divergent findings, likely reflecting their heterogeneity and varying causes. One such condition, melancholia (previously termed endogenous depression), has long held consistent ascriptions: being genetically weighted, having prominent biological perturbations, evidencing overrepresented clinical features, and showing a greater response to physical therapies than to psychotherapy. As psychiatry strives toward a diagnostic nosology based on genetic, behavioral, and neurobiological criteria, melancholia arguably represents a canonical test case.

Historical failure to identify specific neurobiological correlates of melancholia is consistent with recent advances in cognitive neuroscience that regard the brain as a complex network, whereby psychiatric conditions reflect changes in functional integration rather than perturbations within an isolated region. Large-scale brain networks supporting mood regulation, interoception, and cognition (eg, concentration and attention) are thus likely candidates for furthering understanding of melancholia’s neurobiology. The salience network, encompassing the anterior insula (AI) and dorsal anterior cingulate cortex, embodies interactions among interoceptive and cognitive processes that are endowed with an affective or emotional aspect and is hence a candidate target for studying melancholia. For example, following deep brain stimulation of the subgenual cingulate, patients with treatment-resistant depression showed increased blood flow in the AI, highlighting its involvement in mood disturbances. The AI participates in visceral and somatic sensory processing underpinning mood regulation,\(^6\) control of interference during working memory updating,\(^9\) decision making\(^10\) and mediating exchange of salient information to other brain regions, particularly those involved in attention.\(^11\) Frontoparietal attention networks and their relationship to emotional and affective processes have also been well characterized.\(^12-14\) Since disturbances in concentration and attention are well documented in melancholia\(^25\) (the psycho component of its key feature of psychomotor disturbance), examining attention networks provides an opportunity to model this disorder’s neurobiology. In addition to the distinctive anergia that disrupts task completion, patients with melancholic depression report a pervasive dysphoria at rest and difficulties switching between the usual myriad of internal thought processes (eg, memory, planning, and daydreaming). We hence sought to study the integration of resting-state cognitive and emotional networks in individuals with melancholic depression and in appropriate control subgroups.

Failures of functional integration in the brain can be tested by analyses of functional and effective connectivity. Studies\(^45-17\) of functional connectivity (statistical correlations between remote regions) in major depression have shown increased coupling between the default mode network and the anterior cingulate cortex, which is associated with disrupted cognitive processing.\(^18\) Analyses\(^19\) of effective connectivity (inferences regarding causal interactions) indicate decreased connectivity across divergent regions, particularly those involved in attention, salience, and executive processing.\(^20-22\) To date, the specificity of such brain network dysfunction in depressive subtypes has not been addressed.

We examined distinct neural attributes of spontaneously generated thought in melancholia by analyzing resting-state functional magnetic resonance imaging (fMRI) data. We used independent component analysis (ICA) to identify cortical systems or modes underlying cognitive processes, including attention, salience, executive function, and internally generated thought. We applied stochastic dynamic causal modeling (DCM) to infer the patterns of directed effective connectivity between these modes, hypothesizing that melancholia would be characterized by disturbed effective connectivity in networks subserving attention, salience, and interoception.

**Methods**

**Participants**

This observational study was approved by the University of New South Wales Human Research Ethics Committee (approval 08077). Written informed consent was obtained from all participants, and no monetary incentive was provided. Participants included 16 patients with melancholic depression and 16 with nonmelancholic depression, recruited through a specialist depression clinic in Sydney, Australia, between August 30, 2010, and June 27, 2012. All consecutively assessed patients aged between 18 and 75 years meeting a diagnosis of unipolar major depression were referred for possible study inclusion. Toward the end of the recruitment process, some subsampling of the nonmelancholic group was mandated to ensure age and sex matching. A control group of 16 participants, who disavowed any current and/or past mood and/or psychotic illness, was recruited through the community. All participants were screened for current and past mood and psychotic conditions with the Mini-International Neuropsychiatric Interview.\(^23\) Exclusion criteria included hypomania, mania, psychosis, current or past drug or alcohol dependence, neurologic disorder or brain injury, a Wechsler Test of Adult Reading\(^24\) score below 80, and electroconvulsive therapy in the preceding 6 months. Depression severity was quantified with the Quick Inventory of Depressive Symptomatology-16.\(^16\) Participants also completed the State-Trait Anxiety Inventory (STAI-State and STAI-Trait),\(^26\) and overall functioning was measured by the Global Assessment of Functioning scale.\(^27\) We used the CORE measure\(^28\) to assess for psychomotor signs in the depressed participants, with this measure having noninteractivity (ie, cognitive slowing), retardation, and agitation subscales.

**Depression Subtyping Approach**

Clinical diagnoses of melancholic or nonmelancholic depression were made by psychiatrists weighting previously detailed criteria.\(^3-29\) For a diagnosis of melancholia, 2 compulsory criteria were required: psychomotor disturbance (expressed as motor slowing and/or agitation) and an anhedonic mood state. In addition, 5 of the following 9 clinical features were required (and met) in all assigned patients with melancholic depression:

- **Endogenous**
- **Seasonal**
- **Cycloid**
- **Anxiety**
- **Insomnia**
- **Sleep**
- **Hypochondria**
- **Autonomic signs**
- **Somatoform**
cholia: (1) concentration and/or decision-making impairment, (2) nonreactive affect, (3) distinct anergia, (4) diurnal mood variation (being worse in the morning), (5) appetite and/or weight loss, (6) early morning waking, (7) no preceding stressors accounting for the depth of the depressive episode, (8) previous good response to adequate antidepressant therapy, and (9) normal personality functioning. Patient-specific data are provided in eTable 1 in the Supplement.

Deriving Prototypic Melancholic Symptom Profiles
To further characterize our melancholic group, a 32-item Q-sort was completed by all clinical participants to assess the relative weighting of melancholic and nonmelancholic prototypic features. This method requires the sorting of representative items (eg, symptoms) from least to most characteristic (−4 to +4).

Imaging Data Acquisition and Analysis
All participants underwent a 6½-minute resting-state fMRI scan, with the resulting data preprocessed to mitigate head motion and spatially normalized to the standard Montreal Neurological Institute atlas using Statistical Parametric Mapping. Full acquisition, preprocessing, and analysis details are provided in the eAppendix in the Supplement and Figure 1. We identified the key neuronal systems showing spontaneous activity fluctuations in a participant-specific fashion using ICA. High-dimensional spatial ICA was performed in the fMRI Software Library, yielding 70 modes of neuronal, physiologic, and artifactual origin. We chose 5 of these components as being most likely to reflect spontaneous mental activity, namely, the default mode network, executive control (EXC), bilateral anterior insula (INS), and left frontoparietal (LFP) and right frontoparietal (RFP) attention modes. These networks were identified by optimizing the spatial overlap with published resting-state and cognitive maps and ensuring appropriate component selection with visual inspection. The inclusion of the LFP and RFP attentional modes sought to capture cognitive attention (ie, cognitive control systems), which have been shown to correspond to higher-order cognitive domains and are distinct from those involved in attending to visual context (eg, dorsal attention network).

Optimized model parameters from the sDCMs were used for between-group comparisons. The ICA maps are plotted as z statistics and show component intensity from low (black/dark red) to high (yellow/white). DMN indicates default mode network; EXC, executive control; INS, insula, L, left; LFP, left frontoparietal; R, right; and RFP, right frontoparietal.
models using standard (variational) Bayesian techniques, allowing for estimation of the influence of one brain region over another. Although DCM has been widely used to study task-driven effects, recent innovations now permit inferences on effective connectivity in resting-state fMRI by modeling endogenous fluctuations. Our resulting fully connected stochastic DCMs were then optimized to yield a sparse and parsimonious (minimally complex) representation of the network for each participant. These representations (directed and weighted graphs) were used for between-group comparisons, using graphic theoretic measures (average degree and edge strength) as group-dependent variables. Group differences were corrected for multiple measures (5 modes and 20 edges) after accounting for intersubject correlations; further details of these adjustments are provided in the Results section.

**Results**

**Clinical and Demographic Comparisons**

The melancholic, nonmelancholic, and control groups did not differ significantly by age or sex (Table 1). Age ranges for the groups were 20 to 52 years (melancholia), 21 to 56 years (nonmelancholia), and 22 to 75 years (controls; 2 were older than 60 years). Two nonmelancholic participants and 1 healthy control participant were left-handed. The control group reported being on antipsychotic medication ($\chi^2 = 4.57; P = .03$), and their estimated IQ was higher than that of both the melancholic ($t = −2.69; P = .04$) and nonmelancholic ($t = −3.12; P = .004$) groups. The depressed groups did not differ significantly by years of education, Wechsler Test of Adult Reading scores, depression severity, or STAI-State and STAI-Trait scores. Consistent with the diagnostic primacy of psychomotor disturbance, the melancholic group had higher scores compared with the nonmelancholic group on all CORE subscales (noninteractiveness: $t = 3.05; P = .005$; retardation: $t = 3.66; P < .001$; and agitation: $t = 2.55; P = .02$) and higher total CORE scores ($t = 3.93; P < .001$). All groups differed on the Global Assessment of Functioning scale, with the melancholic group having the most severe functional impairment followed by the nonmelancholic group and then the control group participants (Table 1). More nonmelancholic participants reported receiving a selective serotonin reuptake inhibitor (SSRI) antidepressant drug compared with the melancholic participants ($\chi^2 = 5.24; P = .02$); a higher proportion of melancholic participants were receiving non-SSRI medications ($\chi^2 = 8.13; P = .004$). More melancholic participants reported being on antipsychotic medication ($\chi^2 = 4.57; P = .03$).

### Table 1. Demographic and Clinical Characteristics Across Melancholic, Nonmelancholic, and Control Groups

<table>
<thead>
<tr>
<th>Test Variable</th>
<th>Melancholic</th>
<th>Nonmelancholic</th>
<th>Control</th>
<th>Group Comparison*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>38.00 (9.94)</td>
<td>40.44 (10.73)</td>
<td>43.75 (14.10)</td>
<td>t = −0.68 .51 t = −1.33 .19 t = −0.75 .46</td>
</tr>
<tr>
<td>Female sex, No. (%)</td>
<td>8 (50.0)</td>
<td>10 (62.5)</td>
<td>9 (56.3)</td>
<td>$\chi^2 = 0.51 .48 \chi^2 = 0.13 .72 \chi^2 = 0.13 .72$</td>
</tr>
<tr>
<td>Years of education, mean (SD)</td>
<td>14.81 (3.31)</td>
<td>15.88 (2.44)</td>
<td>17.44 (3.58)</td>
<td>t = −1.03 .31 t = −2.15 .04 t = −1.44 .16</td>
</tr>
<tr>
<td>Estimated IQ, mean (SD)</td>
<td>107.93 (12.40)</td>
<td>108.19 (9.96)</td>
<td>117.94 (7.55)</td>
<td>t = −0.06 .95 t = −2.69 .01 t = −3.12 .004</td>
</tr>
<tr>
<td>QIDS-SR, mean (SD)</td>
<td>16.69 (4.22)</td>
<td>15.06 (4.10)</td>
<td>1.19 (1.51)</td>
<td>t = 1.10 .28 t = 13.82 &lt;.001 t = 12.68 &lt;.001</td>
</tr>
<tr>
<td>STAI-State, mean (SD)</td>
<td>49.73 (17.63)</td>
<td>46.25 (12.37)</td>
<td>25.44 (6.52)</td>
<td>t = 0.68 .50 t = 5.42 &lt;.001 t = 5.95 &lt;.001</td>
</tr>
<tr>
<td>STAI-Trait, mean (SD)</td>
<td>55.00 (13.33)</td>
<td>62.88 (8.43)</td>
<td>31.19 (6.45)</td>
<td>t = −1.98 .08 t = 6.27 &lt;.001 t = 11.94 &lt;.001</td>
</tr>
<tr>
<td>GAF, mean (SD)</td>
<td>58.13 (7.04)</td>
<td>69.38 (6.29)</td>
<td>95.00 (0.00)</td>
<td>t = −4.77 &lt;.001 t = −20.95 &lt;.001 t = −16.29 &lt;.001</td>
</tr>
<tr>
<td>CORE, mean (SD)</td>
<td>Noninteractiveness: 3.44 (1.30)</td>
<td>0.75 (1.69)</td>
<td>NA</td>
<td>t = 3.05 .005</td>
</tr>
<tr>
<td></td>
<td>Retardation: 4.88 (3.40)</td>
<td>1.06 (2.41)</td>
<td>NA</td>
<td>t = 3.36 &lt;.001</td>
</tr>
<tr>
<td></td>
<td>Agitation: 0.69 (0.00)</td>
<td>0.00 (0.00)</td>
<td>NA</td>
<td>t = 2.55 .02</td>
</tr>
<tr>
<td>Total: 9.00 (6.12)</td>
<td>1.81 (4.02)</td>
<td>NA</td>
<td>t = 3.93 &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Current medications, No. (%)</td>
<td>No medication: 1 (6.3)</td>
<td>5 (31.3)</td>
<td>NA</td>
<td>t = 3.05 .005</td>
</tr>
<tr>
<td></td>
<td>SSRI: 2 (12.5)</td>
<td>8 (50.0)</td>
<td>NA</td>
<td>t = 3.66 &lt;.001</td>
</tr>
<tr>
<td></td>
<td>Any medication other than SSRI: 13 (81.3)</td>
<td>5 (31.3)</td>
<td>NA</td>
<td>t = 3.66 &lt;.001</td>
</tr>
<tr>
<td></td>
<td>Dual-action antidepressantb: 8 (50.0)</td>
<td>5 (31.3)</td>
<td>NA</td>
<td>t = 3.05 .005</td>
</tr>
<tr>
<td></td>
<td>Tricyclic or monoamine oxidase inhibitor: 4 (25.0)</td>
<td>2 (12.5)</td>
<td>NA</td>
<td>t = 3.50 &lt;.001</td>
</tr>
<tr>
<td></td>
<td>Mood stabilizerc: 1 (6.3)</td>
<td>2 (12.5)</td>
<td>NA</td>
<td>t = 3.05 .005</td>
</tr>
<tr>
<td></td>
<td>Antipsychotic: 4 (25.0)</td>
<td>0</td>
<td>NA</td>
<td>t = 3.05 .005</td>
</tr>
</tbody>
</table>

Abbreviations: GAF, Global Assessment of Functioning; NA, not applicable; QIDS-SR, Quick Inventory of Depressive Symptomatology; SSRI, selective serotonin reuptake inhibitor; STAI, State-Trait Anxiety Inventory.

*Uncorrected P values for between-group comparisons; differences were significant at $P < .05$.

b Serotonin noradrenaline reuptake inhibitor.

c Lithium or valproate/divalproex.

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Analysis of the Q-Sort symptom profiles showed that the 7 items best differentiating melancholic from nonmelancholic participants were (mean difference in ranking): feeling somewhat paralyzed doing basic things (3.67), finding it difficult to do basic things (0.97), feeling physically slowed (0.79), experiencing anticipatory anhedonia (0.57), having lower energy in the morning (0.45), experiencing mood nonreactivity (0.43), and having slowed thinking (0.27).

**Overall Network Effects**
Effective connectivity (node degree effects) among the 5 ICA modes was summarized with their group average in-degree and out-degree (Figure 1) and assessed for significance after adjusting for correlations between dependent variables (mean $r = 0.4$) corresponding to a threshold of $\alpha < .02$.

The melancholic group had markedly diminished inward connectivity (ie, average in-degree) of the RFP (attentional) mode from the other 4 modes (Table 2) in comparison with the nonmelancholic group ($z = 2.93; P = .004$). In particular, single-subject networks in the melancholic group contained, on average, only 1 incoming connection, which was approximately half that of the nonmelancholic group. Participants with melancholia had a significantly diminished outgoing influence of the INS component on other modes compared with the healthy controls ($z = 2.38; P = .02$). The out-degree influence of the INS mode in the nonmelancholic participants was closer to that of healthy controls. A trend-level effect was present for the out-degree of the LFP, with melancholic participants showing fewer outgoing connections compared with nonmelancholic participants ($z = 2.39; P = .02$).

**Specific Effective Connectivity (Group-Averaged Edge Degree) Effects**
Effective connectivity between each pair of the 5 ICA modes was summarized with the corresponding group-averaged value of the edge degree (the proportion of times each specific edge was present in the participant-specific DCMs). Multiple Pearson $\chi^2$ tests were performed on these 20 (nonself) edges and were assessed for significance after adjusting for correlations between dependent variables (mean $r = 0.21$) corresponding to a significance threshold of $\alpha < .005$.

There were 2 significantly reduced connections in the melancholic group (Figure 2 and Table 3), both involving outgoing edges from the INS. The specific influence of the INS component on the RFP mode (INS $\rightarrow$ RFP) was weaker in comparison with the influence in the nonmelancholic group ($\chi^2 = 8.13; P = .004$); INS $\rightarrow$ EXC connectivity was weaker compared with that in the control group ($\chi^2 = 8.96; P = .003$). Both effects were consistent with the decreased overall outgoing influence of the INS in the melancholic group.

No other specific edgewise effects surpassed the corrected statistical threshold. All trend-level differences between the melancholic and nonmelancholic groups involved the LFP and RFP attention modes, with all most reduced in the melancholic group except for LFP self-connectivity, which was increased (Table 3). For complete-

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Table 2. Between-Group Contrasts of Incoming and Outgoing Node Degree for Attentional and Insular Networks

<table>
<thead>
<tr>
<th>Degree Direction and Region</th>
<th>Melancholic (n = 16)</th>
<th>Nonmelancholic (n = 16)</th>
<th>Control (n = 16)</th>
<th>Mann-Whitney</th>
<th>$z$ Value</th>
<th>$P$ Value $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>In, RFP</td>
<td>1.00 (1.03)</td>
<td>2.06 (1.00)</td>
<td>1.63 (0.72)</td>
<td>203.00</td>
<td>2.93</td>
<td>.004 $^b$</td>
</tr>
<tr>
<td>Out, INS</td>
<td>1.81 (1.28)</td>
<td>2.56 (1.26)</td>
<td>2.81 (0.91)</td>
<td>189.00</td>
<td>2.38</td>
<td>.02 $^c$</td>
</tr>
<tr>
<td>LFP</td>
<td>1.50 (1.09)</td>
<td>2.31 (0.87)</td>
<td>2.06 (0.85)</td>
<td>188.50</td>
<td>2.39</td>
<td>.02 $^d$</td>
</tr>
</tbody>
</table>

Abbreviations: INS, insula; LFP, left frontoparietal; RFP, right frontoparietal.

$^a$ Significant differences after (Sidak) familywise error adjustment and correction for correlated outcome variables ($P < .02$).

$^b$ Contrast between melancholic vs control groups.

$^c$ Contrast between melancholic vs nonmelancholic groups.

$^d$ Trend-level difference between melancholic and nonmelancholic groups.
Disrupted Effective Connectivity in Melancholia

Effective Connectivity

Involvement of the INS mode in nonmelancholic participants compared with controls.

Effect of Medications on Network Parameters

Analysis of covariance was used to test for possible medication effects. We split all patient groups into 2 new subsets. First, we compared all patients who were receiving an SSRI with those not receiving an SSRI. Second, we compared patients taking medications other than SSRIs (all broad-spectrum antidepressants, antipsychotics, and mood stabilizers) with patients not receiving any such medications. We controlled for clinical group (melancholic vs nonmelancholic) and analyzed the main network effects observed above (in-degree for RFP and out-degree for both the INS and LFP modes). No significant differences were observed for medication use on the differing network parameters. Formal statistics for all 6 tests are provided in eTable 2 in the Supplement.

Discussion

Whereas disturbances in cognitive and behavioral tasks in individuals with melancholia have been well documented, much of the illness burden is experienced through unpleasant and dysphoric affects during spontaneous thought. Although the quantitative documentation of these phenomena is incomplete, patients with melancholia describe pervasive somatic preoccupation, perseveration of unpleasant themes, and diminished ability to shift attention among spontaneously arising thoughts. Wernicke proposed a theory of brain function whereby higher-order cognitive processes were the result of integration between multiple spatially distributed neuronal systems. Disruption to this integrative architecture (“organs of connection”) hence contributed to disorders such as aphasia and schizophrenia. This theory has become known as the sejunctive hypothesis and emphasizes an anatomical disconnection of axonal processes. Modern formulations of psychiatric “dysconnections” emphasize synaptic abnormalities leading to a more functional and context-sensitive disintegration that is aligned to our findings. A parallel may be drawn between the findings of the present study and schizophrenia, with undirected thought often exacerbating internal preoccupation with abnormal subjective experiences. Analyses of resting-state electroencephalogram and fMRI data has provided fruitful in testing the schizophrenia disconnection hypothesis, yielding evidence of a “subtle but persistent” disconnection. Using stochastic DCM, we studied the neural correlates of spontaneous thought in individuals with melancholia, leveraging recent advances in computational modeling to highlight a novel disconnection syndrome involving attentional and insula-based cortical systems, which differentiated those individuals with melancholic and nonmelancholic depression.

Although our ICA components were derived from resting-state fMRI data, previous work has established close correspondence between resting-state networks and those engaged in classic cognitive tasks. Indeed, we used this correspondence to identify attentional control (LFP and RFP) modes that covary with a variety of cognitive tasks involving modulation of attention, namely, attentional disengagement and reorienting. This focus on dynamic networks relating cognition to spontaneous self-directed thought allows unique insights into the neurobiological features of attentional disturbances in melancholia. For example, a recent study reported that the present sample of melancholic participants exhibited a context-sensitive bias during detection of emotional signals in the presence of uncertainty. It seems reasonable to assert that a qualitatively similar disturbance operates during self-directed thought, leading to an attentional bias toward, and diminished ability to shift away from, negative internal thoughts.

Table 3. Between-Group Edge Connectivity Differences Among Spatially Distributed Brain Networks

<table>
<thead>
<tr>
<th>From Region → Region</th>
<th>Between-Group Contrast</th>
<th>Groups</th>
<th>Proportion Present</th>
<th>Proportion Absent</th>
<th>χ²</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Melancholic</td>
<td>Nonmelancholic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LFP → DMN</td>
<td></td>
<td>0.25</td>
<td>0.62</td>
<td>4.57</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>RFP → INS</td>
<td></td>
<td>0.12</td>
<td>0.50</td>
<td>5.24</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>INS → RFP</td>
<td></td>
<td>0.19</td>
<td>0.69</td>
<td>8.13</td>
<td>.004*</td>
<td></td>
</tr>
<tr>
<td>LFP → LFP</td>
<td></td>
<td>0.75</td>
<td>0.37</td>
<td>4.57</td>
<td>.03</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Groups</th>
<th>Melancholic</th>
<th>Nonmelancholic</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>INS → DMN</td>
<td>0.56</td>
<td>0.87</td>
<td>3.86</td>
</tr>
<tr>
<td>INS → EXC</td>
<td>0.56</td>
<td>1.00</td>
<td>8.96</td>
</tr>
<tr>
<td>EXC → INS</td>
<td>0.75</td>
<td>1.00</td>
<td>4.57</td>
</tr>
<tr>
<td>LFP → RFP</td>
<td>0.25</td>
<td>0.62</td>
<td>4.57</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Groups</th>
<th>Nonmelancholic</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>INS → DMN</td>
<td>0.56</td>
<td>0.87</td>
</tr>
<tr>
<td>INS → EXC</td>
<td>0.75</td>
<td>1.00</td>
</tr>
<tr>
<td>EXC → INS</td>
<td>0.69</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Abbreviations: DMN, default mode network; EXC, executive control; INS, insula; LFP, left frontoparietal; RFP, right frontoparietal.

* Significant after (Sidak) familywise error adjustment and correction for correlated outcome variables ($P < .005$). Additional group differences presented are unadjusted trend-level effects ($P < .05$).
The involvement of the EXC mode is consistent with disturbances in executive function in melancholia, such as biased decision making. Our EXC mode was obtained by comparison with previously published ICA-derived maps that are reliably found in resting-state data and in tasks requiring inhibitory control. However, neuroanatomically, our EXC mode overlapped substantially with portions of the ventromedial prefrontal cortex, which has a variety of affective control functions, including those related to self-reference, affect, and visceral motor regulation. Hence, this mode likely contributes to a range of affective control functions in addition to classic cognitive control.

The AI is a key region in mood regulation, but it also contributes to visceral and somatic sensory processing and mediates the exchange of salient information to other brain regions, particularly those involved in attention. Recent work building on the central role of the AI in interoception, identified an association between weaker functional connectivity of the AI and somatic symptoms of major depression. Our insular component was chosen specifically to incorporate the more anterior regions implicated in interoceptive processes. We observed a diminished outgoing influence of this AI mode in participants with melancholia compared with healthy controls, particularly on the executive mode, which includes key regions (eg, ventromedial prefrontal cortex) subserving affective control mechanisms. Taken together with the diminished connectivity of the RFP mode, this finding provides support for our hypothesis that melancholia is associated with disruptions to key regions underpinning attention and internalized mood state regulation.

Our finding of selective deficits in connectivity from the AI is important in relation to current theoretical neurobiology theories about emotion and self-awareness in terms of interoceptive inference. In these models, the AI is regarded as generating top-down predictions of interoceptive (bodily) states that enslave autonomic (sympathetic and parasympathetic) reflexes that mediate homeostasis. As the AI receives top-down predictions from attentional systems (eg, the frontoparietal mode), these interoceptive predictions are themselves contextualized by high-level representations that become endowed with visceral or affective aspects. In the setting of predictive coding, compromised outflow from the AI to the RFP corresponds to a failure of ascending prediction errors to update (emotional) representations in the prefrontal cortex that may be manifest as somatic preoccupation.

Our finding of disconnectivity of the AI and frontoparietal modes in individuals with melancholia was inferred from modeling effective connectivity and is thus not intended to convey evidence of a neuroanatomical disconnection (in the sejuncture sense). Thus, we propose that fundamental disruptions to neuronal dynamics—rather than a coarse anatomical disconnection—position melancholia as a disorder of connectivity. Dynamic causal modeling rests on relatively rapid, contextually specific changes in synaptic efficacy due to glutamatergic-mediated synaptic activity. This effect is a more subtle network perturbation than the striking correspondence between resting-state networks and gross changes in network anatomy that occur in neurodegenerative disorders. Nonetheless, the present approach is predicated on the same proposed correspondence between neurocognitive syndromes and disturbances in underlying functional networks.

Future work could build on the present findings by addressing several study limitations. Although our sample size is well suited to finding group differences of meaningful effect size, a larger cohort studied in a longitudinal setting would permit several ambiguities to be addressed. First, a larger cohort will allow disentangling of more specific (but more subtle) group differences in specific mode-to-mode influences. Second, a larger cohort may help elucidate the relationship between network changes and illness expression. Quantifying the subjective experience of the resting state through a structured questionnaire could also address the subjective correlates of our observed network effects, particularly against domains such as discontinuity of mind, self, and somatic awareness. Third, our cross-sectional design did not allow us to address whether the observed network changes were evident before the onset of a depressed mood or were state disturbances, limiting inferences about illness causality. Furthermore, because our patient groups differed from healthy controls on estimated IQ, it will be important to clarify the effect of neuropsychological variables on network changes given their relationship to resting-state connectivity. Fourth, the class of prescribed medications differed between our groups, which may have contributed to the findings. Patients within the melancholic group were more likely to be receiving a combination of antidepressants, mood stabilizers, and antipsychotics, precluding regression of single-class dosage equivalence as a nuisance variable. Post hoc analyses, using analysis of covariance to control for diagnosis, suggested that the primary effects reported were unlikely to have been driven by the main medication divisions among our clinical participants (SSRI vs no SSRI and the presence or absence of any non-SSRI medication). We acknowledge the caveats of such a post hoc approach; addressing this finding in future studies will be essential given the differential effects that both antipsychotics and antidepressants have on cerebral blood flow. Although samples of patients not receiving medications would be ideal, the severity of melancholia raises ethical issues regarding the withholding of medication for research purposes. Finally, future analyses of effective connectivity in clinical disorders should incorporate methodologic innovations in stochastic DCM, including alternative approaches to group-level inferences.

Conclusions

We position the neurobiological features of the spontaneous dysphoria of melancholia as a weakening of interactions among regions that subserve attention, mood regulation, and interoception. Computational accounts of internally generated thought highlight the importance of a critical homeostatic balance between stable self-regulation and dynamic instability. We propose that our findings reflect a loss of this optimal balance, undermining the adaptive role of interoception.
Disrupted Effective Connectivity in Melancholia

Original Investigation Research


