Comparison of Functional and Structural Neural Network Features in Older Adults With Depression With vs Without Apathy and Association With Response to Escitalopram
Secondary Analysis of a Nonrandomized Clinical Trial

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Abstract

**IMPORTANCE** Apathy is prevalent among individuals with late-life depression and is associated with poor response to pharmacotherapy, including chronicity and disability. Elucidating brain networks associated with apathy and poor treatment outcomes can inform intervention development.

**OBJECTIVES** To assess the brain network features of apathy among individuals with late-life depression and identify brain network abnormalities associated with poor antidepressant response.

**DESIGN, SETTING, AND PARTICIPANTS** This secondary analysis of a single-group, open-label nonrandomized clinical trial of escitalopram conducted at an outpatient geriatric psychiatry clinic enrolled 40 adults aged 59 to 85 years with major depressive disorder from July 1, 2012, to July 31, 2019.

**INTERVENTIONS** After a 2-week washout period, participants received escitalopram titrated to a target of 20 mg/d for 12 weeks.

**MAIN OUTCOMES AND MEASURES** Baseline and posttreatment magnetic resonance imaging (MRI), clinical, and cognitive assessments were conducted. Functional MRI was used to map group differences in resting state functional connectivity (rsFC) of the salience network, and diffusion MRI connectometry was performed to evaluate pathway-level disruptions in structural connectivity. The Apathy Evaluation Scale was used to quantify apathy, and the Hamilton Depression Rating Scale (HAM-D) was used to quantify the primary outcome of depression severity.

**RESULTS** Forty participants (26 women [65%]; mean [SD] age, 70.0 [6.6] years [range, 59-85 years]) with depression were included; 20 participants (50%) also had apathy. Relative to nonapathetic participants with depression, those with depression and apathy had lower rsFC of salience network seeds with the dorsolateral prefrontal cortex (DLPFC), premotor cortex, midcingulate cortex, and paracentral lobule and greater rsFC with the lateral temporal cortex and temporal pole ($z$ score > 2.7; Bonferroni-corrected threshold of $P < .0125$). Compared with participants without apathy, those with apathy had lower structural connectivity in the splenium, cingulum, and fronto-occipital fasciculus ($t$ score > 2.5; false discovery rate-corrected $P = .02$). Twenty-seven participants completed escitalopram treatment; 16 (59%) achieved remission (HAM-D score <10). Lower insula-DLPFC/midcingulate cortex rsFC was associated with less symptomatic improvement (HAM-D % change) ($β [df] = 0.588 [26]$; $P = .001$) and a higher likelihood of nonremission (odds ratio, 1.041 [95% CI, 1.003-1.081]; $P = .04$) after treatment and, in regression models, was a mediator of the association between baseline apathy and persistence of depression.

(continued)
Lower dorsal anterior cingulate-DLPFC/paracentral rsFC was associated with residual cognitive difficulties on measures of attention ($\beta \ [df] = 0.445 \ [26]; \ P = .04$) and executive function ($\beta \ [df] = 0.384 \ [26]; \ P = .04$).

CONCLUSIONS AND RELEVANCE This study suggests that disturbances in connectivity between the salience network and other large-scale networks that support goal-directed behavior may give rise to apathy and may be associated with poor response of late-life depression to antidepressant pharmacotherapy. These network disturbances may serve as targets for novel interventions.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01728194

Introduction

Late-life depression (LLD) is a leading cause of disability$^1$ and medical morbidity$^2$ in older adulthood. One-third to one-half of patients with LLD also have apathy,$^3$ a persistent and disabling syndrome of impaired motivation characterized by reduced goal-directed behavior, emotional blunting, and cognitive weaknesses.$^4$ Apathy worsens clinical outcomes in LLD. Apathy results in social isolation, poor self-care, and sedentary behavior, with broad health consequences.$^5,10$ Relative to older adults with depression without apathy, those with comorbid apathy are far more likely to withdraw from medical care and have a more severe clinical course, higher caregiver burden, and functional decline.$^6,7$

Remission rates of LLD are especially low among those with prominent apathy.$^11$ Apathy is associated with poor response of depression to selective serotonin reuptake inhibitors (SSRIs), the first-line pharmacotherapy for LLD, and efficacious nonpharmacologic treatment alternatives for this patient population are scarce.$^11-14$ Despite the high prevalence and clinical impact of apathy among individuals with depression, little is known about its optimal treatment and, more broadly, about the brain-based mechanisms of apathy.

An emerging hypothesis suggests that apathy and its impact on treatment response in LLD may reflect compromise of the salience network (SN) and its large-scale network connections.$^5,15,16$ The SN, which includes the insula and dorsal anterior cingulate cortex (dACC), attributes motivational value to a stimulus. The SN dynamically coordinates the activity of other large-scale networks, including the executive control network and default mode network (DMN), to guide purposeful behavior.$^17,18$ The few magnetic resonance imaging (MRI) studies of apathy in depression report reduced volume in structures of the SN and preliminary evidence for disruption in functional connectivity among the SN, DMN, and executive control network.$^3,5,19,20$ Abnormalities within the SN may also predispose older adults with depression to poor response to traditional pharmacotherapies.$^3$ However, the network mechanisms linking apathy to poor antidepressant response in LLD are not well understood.

Identifying network abnormalities in apathy is crucial for understanding its behavioral manifestation in individuals with LLD and for developing new strategies of treatment in clinical practice. Connectometry is a novel approach to diffusion MRI analysis that quantifies the local connectome of white matter pathways.$^{21}$ Connectometry is less susceptible to crossing fibers and partial volume effects and offers greater localization of microstructural abnormalities compared with conventional tract-based analysis$^{21-25}$ but, to our knowledge, has not yet been applied to the study of apathy. Moreover, connectometry can be used alongside resting state imaging to identify network properties of apathy in major depression.

Our primary objective was to evaluate functional connectivity and structural network disturbances associated with apathy in older adults with LLD. Informed by our conceptual
framework, we focused on functional connectivity of the SN and hypothesized alterations in connectivity among key nodes of the SN and other core circuits that modulate goal-directed behavior (ie, DMN, executive control network) among individuals with depression and apathy. We further applied connectometry to identify pathway-level disruptions in structural connectivity and hypothesized that compromise of frontoparietal and frontolimbic pathways would be associated with apathy in LLD. Our secondary objective was to evaluate whether apathy-related network abnormalities were associated with antidepressant response after 12 weeks of pharmacotherapy with the SSRI escitalopram. Therefore, we assessed whether pretreatment variability in connectivity associated with apathy was associated with mood and cognitive outcomes after antidepressant treatment.

Methods

Participants
The study, conducted at an outpatient geriatric psychiatry clinic from July 1, 2012, to July 31, 2019, included participants aged 59 to 85 years who met Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV) criteria for major depressive disorder without psychotic features. Participants were recruited for a single-group, open-label escitalopram treatment trial (NCT01728194) through advertisements and clinical referrals. Participants provided written informed consent approved by the Weill Cornell Medicine and Nathan Kline Institute institutional review boards. Exclusion criteria were current or lifetime history of any Axis I psychiatric disorder other than major depressive disorder or comorbid generalized anxiety disorder, high suicide risk, history of electroconvulsive therapy, ongoing treatment with medications associated with depression (eMethods in Supplement 1), acute or severe medical illness, mild cognitive impairment or dementia, history of neurologic disease, and contraindications to undergoing MRI. The study and data are presented according to the Transparent Reporting of Evaluations With Nonrandomized Designs (TREND) reporting guideline for nonrandomized clinical trials.26

Diagnostic Assessments
A DSM-IV diagnosis was assigned by a study clinician based on the Structured Clinical Interview for DSM-Revised,27 and inclusion required a Hamilton Depression Rating Scale (HAM-D) score of 18 or more (range, 0-76, where 0 indicates no depression and 76 indicates severe depression).28 Mild cognitive impairment was assessed using the Petersen criteria29 and determined using a previously described classification procedure.30 Although the primary outcome for the main clinical trial was the Montgomery-Asberg Depression Rating Scale score, several items capture core features of apathy (Montgomery-Asberg Depression Rating Scale dysphoric apathy subscale).31,32 Therefore, the HAM-D score was chosen as the primary depression outcome in the secondary analysis presented here.

Apathy was evaluated using the clinician-rated version of the Apathy Evaluation Scale,33-35 a psychometrically validated instrument consisting of 18 items rated on a Likert scale.33,36,37 Total scores range from 18 to 72, with higher scores corresponding to more severe symptoms. An examination of the psychometric properties of the Apathy Evaluation Scale found that cutoff values greater than 40.5 and 37.533 had similar sensitivity (88%), although a higher cutoff value had better specificity.34 Accordingly, an Apathy Evaluation Scale score of more than 40.5 was considered a priori to represent clinically significant apathy.34,35

Neuropsychological Assessment
A focused neuropsychological assessment conducted at baseline and after treatment included measures of processing speed, attention, memory, language, and executive functioning. This study focused on measures of attention (Digit Span Forward; Wechsler Adult Intelligence Scale, Fourth Edition) and executive function (Stroop Interference38 and Trail Making Test Part B − A) because they
are commonly impaired among individuals with LLD and deficits often persist after antidepressant treatment.39,40

**Treatment Protocol**

Participants previously prescribed an antidepressant underwent a 2-week washout period under the care of a study psychiatrist. Those who remained eligible after the 2 weeks were treated with escitalopram for 12 weeks: 10 mg/d for 1 week, followed by an increase to the target dose of 20 mg/d. Participants unable to tolerate 20 mg/d received either 15 mg/d or 10 mg/d, which was the minimum study dose, for the remainder of their participation. Participants completed weekly assessments of depression and side effects41 with trained research assistants and a research psychiatrist (eMethods in Supplement 1).

**Image Processing**

Structural T1, diffusion-weighted, and T2-weighted blood oxygen level–dependent functional imaging data were acquired on a 3T Siemens Tim Trio MRI scanner. Acquisition parameters have been previously reported30,38 and are described along with preprocessing pipelines in the eMethods in Supplement 1.

A hypothesis-driven seed-to-whole-brain approach was used to test for group differences in resting state functional connectivity (rsFC) of the SN between participants with depression and apathy and those with depression without apathy. The left and right insula and dACC—core SN hubs—were used as a priori seed regions generated from the Human Connectome Project–derived Glasser Parcellation Atlas.42 Individual rsFC maps for SN seeds were generated based on correlations between the mean signal time course within each seed region and each voxel of the brain. Group-level inferential models were conducted to compare the seed-based connectivity maps of participants with and without apathy. We implemented cluster-based inference using Gaussian random field theory with a height z score greater than 2.343-48 and a Bonferroni cluster correction of \( P < .0125 \) (2-tailed) to account for the number of seeds analyzed (n = 4).

Diffusion connectometry21 was applied to derive the correlational tractography showing an association between quantitative anisotropy and apathy.49,50 Connectometry measures the degree of connectivity between adjacent voxels based on the density of diffusing spins and probes group differences within subcomponents of white matter pathways.21 The tensor metrics were calculated, and quantitative anisotropy was extracted as the local connectome fingerprint.51 A t score threshold of 2.5 was assigned and tracked using a deterministic fiber tracking algorithm,52 and connectometry was performed across the whole brain, excluding the cerebellum.53,54 To estimate the false discovery rate (FDR), 10 000 randomized permutations were applied to the group label to obtain the null distribution of the track length. An FDR threshold of less than .05 was used to correct for multiple comparisons.21,52

**Statistical Analysis**

The t test, the Mann-Whitney test, and the \( \chi^2 \) test were used to identify individual demographic and clinical variables that distinguished participants with depression without apathy from those with depression and apathy. \( \beta \) weights and quantitative anisotropy values were extracted from significant clusters and fascicles that differed between groups in rsFC and connectometry analyses, respectively, to evaluate associations with clinical outcomes. Change in mood (HAM-D score) was the primary outcome, and change in attention and executive function served as secondary outcomes. Linear and logistic regression models were generated to evaluate whether group differences in baseline connectivity were associated with symptom change (percentage change in HAM-D score) and remission of depression (HAM-D score <10),55 adjusting for age and baseline depression severity. Secondary linear regression models assessed the associations between baseline connectivity and change in performance (posttreatment \( T_2 \) − baseline \( T_1 \)) on measures of attention (Digit Span Forward) and executive functioning (Trail Making Test Part B-A and Stroop Interference), adjusting...
for age, educational level, baseline depression severity (HAM-D score), and baseline task performance.

In models with significant associations between baseline connectivity and treatment response, exploratory post hoc mediation analyses were performed to assess whether the association between presence of apathy and antidepressant response was mediated by apathy-associated abnormalities in connectivity. To estimate the indirect effect, bootstrapping (k = 5000 samples) was used to generate 95% CIs. Mediation results are considered significant if the 95% CI for the indirect path does not contain zero. Mediation models were fit in PROCESS, version 3.4.57 for SPSS, version 26 (IBM SPSS).

Results

Sample Characteristics
Forty older adults (26 women [65%]; mean [SD] age, 70.0 [6.6] years [range, 59-85 years]) with major depressive disorder were evaluated, of whom 20 had apathy at the prespecified threshold (Apathy Evaluation Scale score >40.5). Groups did not differ significantly in age, sex, educational level, or baseline depression severity (Table 1).

Functional Connectivity of the SN in Apathy
Compared with participants with depression alone, those with depression and apathy showed lower rsFC between the left insula seed and the right dorsolateral prefrontal cortex (DLPFC), midcingulate cortex (MCC), and premotor cortex (mean z score = 2.82; Bonferroni-corrected threshold of \( P < .0125 \)) (eTable in Supplement 1). Connectivity of the left insula with the left temporal pole and middle temporal gyrus was significantly greater in participants with apathy than those without apathy (mean z score = 2.78; Bonferroni-corrected threshold of \( P < .0125 \)) (Figure 1). Using the right insula seed, no significant group differences were observed.

Table 1. Demographic and Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total sample (N = 40)</th>
<th>LLD (n = 20)</th>
<th>Apathy and LLD (n = 20)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Age, mean (SD), y</td>
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<td>71.3 (6.9)</td>
<td>68.8 (6.1)</td>
<td>.23</td>
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<tr>
<td>Sex, No. (%)</td>
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<td></td>
</tr>
<tr>
<td>Female</td>
<td>26 (65)</td>
<td>14 (70)</td>
<td>12 (60)</td>
<td>.74</td>
</tr>
<tr>
<td>Male</td>
<td>14 (35)</td>
<td>6 (30)</td>
<td>8 (40)</td>
<td></td>
</tr>
<tr>
<td>Educational level, mean (SD), y</td>
<td>14.9 (2.9)</td>
<td>14.9 (2.4)</td>
<td>14.9 (3.4)</td>
<td>.96</td>
</tr>
<tr>
<td>AES score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>39.9 (6.7)</td>
<td>34.4 (3.6)</td>
<td>45.6 (3.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Range</td>
<td>28-53</td>
<td>28-40</td>
<td>41-53</td>
<td></td>
</tr>
<tr>
<td>24-item HAM-D score, mean (SD)</td>
<td>24.2 (3.9)</td>
<td>23.2 (3.2)</td>
<td>25.2 (4.2)</td>
<td>.11</td>
</tr>
</tbody>
</table>

Abbreviations: AES, Apathy Evaluation Scale (clinician-rated version); HAM-D, Hamilton Depression Rating Scale; LLD, late-life depression.

Figure 1. Differences in Functional Network Connectivity Associated With Apathy in Older Adults With Depression

Group differences in seed-to-whole-brain functional connectivity of the left insula. Blue indicates clusters with lower connectivity with the left insula seed in participants with depression and apathy compared with participants with depression alone. Yellow indicates clusters with higher connectivity with the left insula seed in participants with apathy and depression. Cluster-based inference was implemented using Gaussian random field theory with a Bonferroni cluster correction of \( P < .0125 \) (2-tailed).
Participants with depression and apathy showed lower rsFC between the right dACC seed and the right DL-PFC, paracentral lobule (PCL), and anterior premotor cortex compared with participants with depression alone (mean z score = 3.0; Bonferroni-corrected threshold of P < .0125) (eFigure 1 in Supplement 1). Participants with apathy also showed greater rsFC between the right dACC and the left lateral temporal cortex (mean z score = 2.72; Bonferroni-corrected threshold of P < .0125). There were no group differences in connectivity using the left dACC seed.

**Structural Connectivity in Apathy**

Connectometry analysis identified decreased structural connectivity (quantitative anisotropy) in the splenium of the corpus callosum, cingulum, and left inferior fronto-occipital fasciculus among participants with apathy compared with nonapathetic participants (t score > 2.5, FDR-corrected P < .05) (eFigure 2 in Supplement 1). There were no areas in which quantitative anisotropy was significantly higher among those with comorbid apathy.

**Associations Between Baseline Connectivity and Antidepressant Response**

Twenty-seven participants completed the trial; 16 (59%) achieved remission (HAM-D score < 10). Adjusting for age and baseline depression severity, lower insula-DLPFC/MCC connectivity at baseline was associated with less reduction in depressive symptoms (percentage change in HAM-D score) (β [df] = 0.588 [26]; P = .001) (Table 2) and a higher likelihood of nonremission (HAM-D score < 10) after treatment (odds ratio, 1.041 [95% CI, 1.003-1.081]; B [SE] = 0.04 [0.019]; P = .04) (Figure 2).

There was no significant association between dACC connectivity and change in HAM-D score. However, there were positive associations between dACC-DL-PFC/PCL connectivity and change in cognitive performance. Specifically, lower baseline dACC-DL-PFC/PCL connectivity was associated with less improvement (stable or reduced performance) on measures of attention (β [df] = 0.445 [26]; P = .04) and executive function (β [df] = 0.384 [26]; P = .04) (Stroop Interference), while greater connectivity was associated with greater improvement in performance after treatment (eFigure 3 in Supplement 1). Baseline group differences in structural connectivity were not significantly associated with mood or cognitive outcomes.

Exploratory post hoc mediation analysis showed that the presence of apathy at baseline was associated with a poorer antidepressant response (lower percentage change in HAM-D score) after treatment (c path; β = -0.933; P = .02). There was an association between apathy and insula-DL-PFC/MCC connectivity (a path; β = -1.20; P = .002), which was expected as connectivity was defined by its association with apathy in the baseline sample. There was also a significant indirect effect of insula connectivity, suggesting that group differences in insula-DL-PFC/MCC connectivity mediated the association between apathy and treatment response (indirect effect β = -0.586; bootstrapped 95% CI, -1.477 to -0.072). Path coefficients indicate that baseline apathy was

### Table 2. Parameter Estimates From Linear Regression Models Assessing Associations Between Pretreatment Salience Network Connectivity and Antidepressant Treatment Response

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unstandardized B (95% CI)*</th>
<th>β Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insula-DL-PFC/MCC connectivity</td>
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<td></td>
<td></td>
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<tr>
<td>HAM-D</td>
<td>48.3 (21.3 to 75.2)</td>
<td>0.588</td>
<td>.001</td>
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<tr>
<td>DSF</td>
<td>-0.02 (-2.22 to 2.16)</td>
<td>-0.005</td>
<td>.98</td>
</tr>
<tr>
<td>Stroop Interference</td>
<td>4.23 (-2.6 to 11.10)</td>
<td>0.215</td>
<td>.21</td>
</tr>
<tr>
<td>Trail Making Testb</td>
<td>0.06 (-0.43 to 0.55)</td>
<td>0.064</td>
<td>.79</td>
</tr>
<tr>
<td>dACC-DL-PFC/PCL connectivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAM-D</td>
<td>27.01 (-13.37 to 67.38)</td>
<td>0.283</td>
<td>.18</td>
</tr>
<tr>
<td>DSF</td>
<td>2.7 (0.12 to 5.20)</td>
<td>0.445</td>
<td>.04</td>
</tr>
<tr>
<td>Stroop Interference</td>
<td>8.8 (0.52 to 17.10)</td>
<td>0.384</td>
<td>.04</td>
</tr>
<tr>
<td>Trail Making Testb</td>
<td>-0.34 (-0.90 to 0.22)</td>
<td>-0.330</td>
<td>.22</td>
</tr>
</tbody>
</table>

Abbreviations: dACC, dorsal anterior cingulate cortex; DL-PFC, dorsolateral prefrontal cortex; DSF, Digit Span Forward; HAM-D, Hamilton Depression Rating Scale; MCC, midcingulate cortex; PCL, paracentral lobule.

* HAM-D, DSF, and Stroop Interference regression model df = 26. The HAM-D reflects the percentage change in HAM-D score from baseline to posttreatment.

b Trail Making Test regression model df = 21. The Trail Making Test reflects the change in difference in duration between Part A and Part B (B - A) from baseline to posttreatment.
associated with lower insula-DLPFC/MCC connectivity which, in turn, was associated with poorer antidepressant response (see the eResults in Supplement 1 for post hoc sensitivity analyses).

Discussion

The principal finding of this study is that, relative to participants with depression alone, those with depression and apathy showed alterations in rsFC between the SN and large-scale networks that support goal-directed behavior (DMN and executive control network) and compromised structural connectivity in a core set of brain circuits. Moreover, apathy-related alterations in rsFC were associated with reduced symptomatic improvement and a lower likelihood of remission of depression, as well as persistent cognitive dysfunction, after 12 weeks of treatment with escitalopram.

These findings support an emerging model of apathy, which proposes that apathy may arise from dysfunctional interactions among core networks (ie, SN, DMN, and executive control) that support motivated behavior.58-60 Evidence for this model has been derived largely from studies of neurodegenerative disorders and stroke,12,14,61 leaving the mechanisms underlying motivational disturbances among individuals with depression poorly understood.

In a sample of older adults with LLD, those with comorbid apathy showed reduced rsFC between the SN and the DLPFC, a key node of the executive control network, as well as the prefrontal cortex and PCL. The SN communicates with the executive control network to mobilize the cognitive resources required for goal-directed behavior58,62 and sends signals to primary and secondary motor cortices to facilitate action initiation.53,64 Functional disconnection between the SN and DLPFC may indicate reduced synchrony of systems supporting attentional control, working memory, and cognitive flexibility—core processes disrupted in apathy.8,60,65 Moreover, altered communication between the SN and motor systems may result in difficulties translating intention into action.66 These observations converge with reports in healthy adults showing associations between disturbances in rsFC between the SN and executive control network and reduced motivation,67,68 as well as work linking lower rsFC between the dACC and supplementary motor area to apathy among community-dwelling adults.66

Figure 2. Associations Between Baseline Functional Connectivity and Antidepressant Treatment Response

A, Lower pretreatment insula–dorsolateral prefrontal cortex (DLPFC)/midcingulate cortex (MCC) connectivity, which was associated with presence of apathy at baseline, was associated with greater persistence of depression (lower percentage change in Hamilton Depression Rating Scale [HAM-D] score) after treatment (β = 0.588; ΔR² = 0.34). The R² value indicates the change in variance that is explained (ΔR²) when functional connectivity is added to the regression model adjusted for age and baseline depression severity (HAM-D score). The shaded area indicates SE. B, Lower insula-DLPFC/MCC connectivity at baseline was associated with a higher likelihood of nonremission of depression (HAM-D score <10) after treatment (odds ratio, 1.041 [95% CI, 1.003-1.081]; P = .04). The box plot depicts insula-DLPCF/MCC connectivity of participants who did not achieve remission and participants who achieved remission. The median is denoted by the line within the box; 25th percentile, bottom border of box; 75th percentile, top border of box; variability outside the IQR, whiskers; and outside values, dots.
Participants with apathy and depression also showed higher rsFC between SN seeds and the dorsal medial subsystem of the DMN. In response to salient stimuli, the SN generates control signals that downregulate the DMN in favor of task-positive networks, such as the executive control network. Increased rsFC with the SN may reflect difficulty modulating or disengaging the DMN, affecting the ability to generate cognitive strategies necessary for motivated behavior while ignoring irrelevant or internally directed stimuli. Consistent with this model, failure to suppress the DMN is associated with lapses in attention and decreased cognitive control performance, core features associated with apathy. These findings also align with a prior preliminary study showing increased rsFC between the insula and nodes of the DMN among participants with depression and apathy relative to healthy older adults.

Along with functional network abnormalities, we applied diffusion connectometry to evaluate pathway-level disruptions in structural connectivity associated with apathy. Participants with comorbid apathy showed lower structural connectivity in the splenium, left inferior fronto-occipital fasciculus, and cingulum than those without apathy. The cingulum enables communication between the cingulate cortex, parietal, and medial temporal regions, and integrity of this pathway has been associated with processes disrupted in apathy, including affective processing, decision-making, and behavioral initiation. The fronto-occipital fasciculus connects frontal, insular, occipital, and parietal regions, and the splenium is a commissural tract that connects the posterior parietal, temporal, and occipital cortices. Efficient transmission of sensory information to the SN is needed to identify salient stimuli and guide goal-directed behavior. Microstructural abnormalities in these pathways may reduce interhemispheric communication and the integration of sensory signals with frontal and insular structures. Thus, along with frontolimbic fibers, compromise of pathways that facilitate the transmission of sensory signals for salience processing may be associated with the apathy trait.

More broadly, these findings collectively suggest that apathy among individuals with LLD may be associated with disturbances in SN modulation of large-scale circuits (DMN and executive control network) to facilitate goal-directed behavior. This may cause a failure of network integration, leading to difficulties with salience processing, action planning, and behavioral initiation that manifests clinically as apathy.

Select circuit abnormalities associated with apathy at baseline were also associated with individual differences in response to an SSRI treatment trial. Specifically, low pretreatment insula-DLPFC/MCC connectivity was associated with reduced response and remission of depression, while low dACC-DLPFC/PCL connectivity was associated with residual cognitive difficulties on measures of attention and executive function. In exploratory analyses, lower insula-DLPFC/MCC connectivity mediated the association between presence of apathy and poor antidepressant response. Thus, apathy-related variability in rsFC may predispose older adults with depression to persistent mood and cognitive deficits after traditional antidepressant pharmacotherapy. These data suggest that the effectiveness of SSRI treatment in LLD may rely on an intact ability to detect and transmit signals of salience, and highlight SN-executive control network connectivity as a potential therapeutic target for novel interventions.

Limitations
This study has several limitations. There was no longitudinal follow-up after acute treatment and a relatively limited neuropsychological battery, so we cannot establish the persistence of treatment differences nor the specificity of cognitive associations. Although we attempted to exclude participants with mild cognitive impairment, it is possible that some participants may have had mild cognitive impairment that was not detected by our evaluation process. In addition, the study sample size is relatively small and was reduced at follow-up. As such, the longitudinal findings, including the post hoc mediation analyses, should be considered preliminary. Follow-up studies with larger samples using multiple cognitive measures and a more comprehensive diagnostic assessment of apathy will increase confidence in our results. There are also opportunities to optimize our imaging
The functional MRI scan was relatively short based on current standards, and a longer multiband acquisition would improve the precision of signal estimation. For cluster-based analyses, we applied a threshold commonly used in clinical trials and studies with modest sample sizes, although a more conservative threshold would further reduce the risk of type I error. We applied a hypothesis-driven, seed-to-whole-brain rsFC approach focused on the SN. Future studies evaluating other networks that may be disrupted in apathy, including the reward network, will provide further insights into its etiopathogenesis.

Conclusions

This secondary analysis of a nonrandomized clinical trial suggests that disturbances in connectivity among a core set of brain networks that support motivated behavior (SN, DMN, and executive control network) may give rise to apathy and predispose depressed older adults to poor response to first-line pharmacotherapies. These findings contribute to our understanding of the functional neuroanatomy of motivational disturbances in depression and the network pathways linking apathy to poor clinical outcomes in LLD. Novel interventions that modulate interactions among affected circuits may help to improve clinical outcomes in this distinct subgroup of older adults with depression, for whom few effective treatments exist.
grants from the National Institute of Mental Health during the conduct of the study and grants from Akili Interactive. No other disclosures were reported.

**Funding/Support:** This work was supported by grants R01 MH097735 (Dr Gunning) and T32 MH019132-30 (Dr Alexopoulos) from the National Institute of Mental Health.

**Role of the Funder/Sponsor:** The National Institute of Mental Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Data Sharing Statement:** See Supplement 2.

**REFERENCES**


SUPPLEMENT 1.

eMethods.
eResults.

eTable. Coordinates (MNI) of Clusters That Differed in Functional Connectivity With Salience Network Seeds Between Participants With and Without Apathy

eFigure 1. Differences in Dorsal Anterior Cingulate (dACC) Connectivity Associated With Apathy in Older Adults With Depression

eFigure 2. Differences in Structural Connectivity Associated With Apathy in Older Adults With Depression

eFigure 3. Associations Between Pretreatment Dorsal Anterior Cingulate Cortex (dACC) Connectivity and Change in Cognitive Performance Following Escitalopram Treatment

eReferences.

SUPPLEMENT 2.

Data Sharing Statement