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Functional Connectivity in the Cognitive Control Network and the Default Mode Network in Late-life Depression

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Abstract

Background—Abnormalities have been identified in the Cognitive Control Network (CCN) and the default mode network (DMN) during episodes of late-life depression. This study examined whether functional connectivity at rest (FC) within these networks characterize late-life depression and predict antidepressant response.

Methods—26 non-demented, non-MCI older adults were studied. Of these, 16 had major depression and 10 had no psychopathology. Depressed patients were treated with escitalopram (target dose 20 mg) for 12 weeks after a 2-week placebo phase. Resting state timeseries was determined prior to treatment. FC within the CCN was determined by placing seeds in the dACC and the DLPFC bilaterally. FC within the DMN was assessed from a seed placed in the posterior cingulate.

Results—Low resting state FC within the CCN and high FC within the DMN distinguished depressed from normal elderly subjects. Beyond this “double dissociation”, low resting state FC within the CCN predicted low remission rate and persistence of depressive symptoms and signs, apathy, and dysexecutive behavior after treatment with escitalopram. In contrast, resting state FC within the DMN was correlated with pessimism but did not predict treatment response.

Conclusions—If confirmed, these findings may serve as a signature of the brain’s functional topography characterizing late-life depression and sustaining its symptoms. By identifying the

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CONFLICTS OF INTEREST

Dr. Alexopoulos received grant support from Forest Pharmaceuticals and has been a member of speakers’ bureaus of Astra Zeneca, Avanir, Forest, Merck, and Lundbeck. He holds equity of Johnson and Johnson. Dr. Lim serves on the Scientific Advisory Board for Shire Corp, a biopharmaceutical company. No other authors report conflicts of interest.

Contributors

Dr. Alexopoulos conceptualized and designed and oversaw the conduct of the study, obtained funding and wrote the first draft of the manuscript. Dr. Hoptman oversaw acquisition of MRI data. Drs. Lim and Hoptman guided image analysis and provided consultation on data interpretation. Dr. Gunning performed processing and analysis of MR images and contributed to revisions of the manuscript for important technical and intellectual content. Ms. Kanellopoulos developed and managed the research database and performed statistical analyses in SPSS and SAS and contributed to the interpretation of data. Dr. Murphy aided in the design of the study and oversaw the collection of data. All authors contributed to the manuscript and have approved the final version.

network abnormalities underlying biologically meaningful characteristics (apathy, dysexecutive behavior, pessimism) and sustaining late-life depression, these findings can provide a novel target on which new somatic and psychosocial treatments can be tested.

INTRODUCTION

Structural and functional abnormalities have been identified in depressed older adults in structures participating in cognitive and emotional regulation. In the cognitive control network (CCN), microstructural white matter abnormalities have been found in structures including the dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate cortex (ACC) (Alexopoulos et al., 2009, Bae et al., 2006). Decreased metabolic activity at rest has been observed in the dorsal ACC and the DLPFC during episodes of depression(Drevets et al., 1997, Mayberg et al., 1999, Aizenstein et al., 2009). When challenged with tasks probing the CCN both elderly (Aizenstein et al., 2009) and young (Fales et al., 2008) depressed patients exhibit decreased DLPFC activation. This hypoactivation of the DLPFC resolves after SSRI treatment (Aizenstein et al., 2009, Fales et al., 2009), but decreased task-based FC may persist(Aizenstein et al., 2009). Further, abnormalities in CCN structures during episodes of late-life depression may influence response to antidepressants(Alexopoulos et al., 2008).

A complex network of corticolimbic structures have been implicated in emotional regulation. Among these structures, ventromedial prefrontal regions play a prominent role in depression. For example, lesions in the ventromedial prefrontal cortex (VMPFC) are associated with abnormal affect-guided anticipation and planning (Damasio, 1994). Failure to anticipate and direct behavior towards positive incentives leads to “negativity bias”, a common behavioral characteristic of depressed patients. Posterior cingulate cortex pathways devoted to attentional processing, and amygdalar pathways devoted to emotional processing converge within the ventral ACC (BA24)(Davidson et al., 2002). Abnormal activation of the ventral ACC (BA24 and BA32) may be associated with blunted conscious experience of affect, hypoarousal, anhedonia, reduced coping in situations of uncertainty, conflict, and expectancy violation between the environment and the individual’s affective state(Davidson et al., 2002). Metabolic increases that occur in the ventral ACC during depressive episodes, correlate with symptom severity(Drevets et al., 1997, Mayberg et al., 1999). Further, remission of depression has been associated with metabolic changes in structures participating in emotional regulation (e.g., amygdala, ventral ACC)(Bauer et al., 2005, Drevets, 1999, Lopez-Sola et al., 2010, Mayberg et al., 2005).

Depressed elders have cortical and subcortical microstructural white matter abnormalities (Alexopoulos et al., 2009, Gunning-Dixon et al., 2008) and greater white matter hyperintensity (WMH) burden within and connecting networks critical for cognitive control and emotional regulation (e.g., the uncinate, superior and inferior longitudinal, and fronto-occipital fasciculi, and external capsule) (Sheline et al., 2008). Further, in elderly depressed subjects microstructural white matter abnormalities in emotional regulation and cognitive control systems are associated with poor antidepressant response(Alexopoulos et al., 2008), and reduced task-based in FC in the CCN persists despite treatment with an SSRI(Aizenstein et al., 2009). Further, recent data indicate that greater WMH burden is associated with hyperactivation of the subgenual cingulate in late-life depression(Aizenstein et al., 2011).

Taken together, the above findings suggest that corticolimbic connectivity, particularly in networks associated with emotional regulation and cognitive control, plays a role in geriatric depression. These observations are mainly derived from structural imaging and from studies of cerebral activation in response to specific tasks. However, late-life depression is a complex disorder with symptoms mediated by large distributed networks. Arguably,

assessment of the brain's functional connectivity (FC) at rest can offer complementary information on relationships among structures with abnormal activation patterns during depression.

FC is based on the observation that spontaneous blood oxygen level dependent (BOLD) signal fluctuations among brain regions similarly modulated by specific tasks tend to be correlated(Fox et al., 2009, Biswal et al., 1995, Cordes et al., 2001, Cordes et al., 2000, De Luca et al., 2005, Fox et al., 2006, Fox and Raichle, 2007, Lowe et al., 1998, Xiong et al., 1999). FC during rest is thought to reflect important interrelationships among structures with related functions. Most of the brain's energy (>85%) is consumed to maintain a functionally differentiated state at rest(Fox and Raichle, 2007). Studies using differing methodology suggest that BOLD activity during a resting state is mainly driven by "intrinsic activity", which remains consistent across different resting conditions(Fransson, 2005, Raichle and Mintun, 2006), task performance(Arfanakis et al., 2000, Arieli et al., 1996, Bartels and Zeki, 2005, Engel et al., 2001, Fair et al., 2007, Fransson, 2006, Greicius et al., 2004, Grill-Spector et al., 2004, Hampson et al., 2004, Jiang et al., 2004, Lowe et al., 2000, Marder and Weimann, 1991, Morgan and Price, 2004, Pessoa et al., 2002, Pessoa and Padmala, 2005, Ress et al., 2000, Ress and Heeger, 2003, Sapir et al., 2005, Sun et al., 2007, Tsodyks et al., 1999, Wagner et al., 1998, Waites et al., 2005), sleep(Fukunaga et al., 2006, Horovitz et al., 2008), and anesthesia (Peltier et al., 2005, Vincent et al., 2007).

This study focuses on FC within the CCN (dorsal ACC, DLPFC, parts of the parietal lobe) and the default mode network (DMN) (posterior cingulate/precuneus, VMPFC, ventral ACC, inferior lateral parietal lobes, and parts of the temporal lobe). It targets the CCN because anatomical and functional abnormalities of its structures have been identified in late-life depression and because some of these abnormalities have been linked to poor response to antidepressants(Alexopoulos et al., 2008, Alexopoulos et al., 2009, Gunning-Dixon et al., 2008) The DMN consists of regions that consistently decrease their activity during cognitive task performance(Fox and Raichle, 2007, Raichle and Snyder, 2007). These same regions are more active at rest than during task performance. Beyond maintaining processes of the brain's resting state (Raichle et al., 2001), structures of the DMN are central to affect regulation and have been found excessively activated during depressive episodes (Sheline et al., 2009). Many of the DMN structures participate in emotional regulation. Accordingly, this study tested the hypothesis that low resting state FC within the CCN and high FC within the DMN distinguishes depressed from normal older adults. An additional hypothesis was that lower FC of the CCN during depressive episodes predicts persistence of depressive symptoms and signs during treatment with a selective serotonin reuptake inhibitor (SSRI).

METHODS

Subjects

We studied depressed and non-depressed adults aged 60 years and older. The depressed group consisted of consecutively recruited subjects who met DSM-IV criteria for unipolar major depression without psychotic features and had a score of 18 or greater on the 24-item Hamilton Depression Rating Scale (HDRS)(Hamilton, 1960). The normal comparison subjects were recruited through advertisement and were required to have no history or presence of any psychiatric disorder. The subjects signed written informed consent approved by the IRBs of Weill-Cornell Medical College and of Nathan Kline Institute.

Individuals were excluded if they had: 1) Mini-Mental State Examination score < 24 (Folstein et al., 1975) or met the mild cognitive impairment (MCI) criteria of Petersen et al (Petersen, 2004) during the clinical interview; 2) presence of delirium, history of stroke,

head trauma, multiple sclerosis, or brain degenerative diseases; 3) metastatic cancer, brain tumors, unstable cardiac, hepatic, or renal disease, myocardial infarction, or stroke within the 3 months preceding the study; 4) diseases frequently associated with depression, i.e. lymphoma, pancreatic cancer, or endocrinopathies other than diabetes; 5) treatment with drugs associated with depression, i.e. steroids, alpha-methyl-dopa, clonidine, reserpine, tamoxifen, or cimetidine; and 6) metal implants. Depressed subjects with history of other axis I psychiatric disorders prior to the onset of depression were excluded.

Assessment

DSM-IV diagnosis was based on the SCID-R, administered at entry to the study. Depressive symptoms were assessed using the Montgomery Asberg Depression Rating Scale (MADRS). Overall cognitive impairment was rated with the Mini Mental State Examination (MMSE)(Folstein et al., 1975) and the Dementia Rating Scale (Mattis, 1989). Response inhibition was assessed with the Stroop Color Word Test (Golden, 1978), visual attention and task switching with Trails A and Trails B (Reitan, 1985) and and dysexecutive behavior with the Frontal Systems Behavior Scale (FrSBe)(Grace J, 2001). Apathy was quantified with the Apathy Evaluation Scale(Marin et al., 1991). Memory was rated with the Hopkins Verbal Learning Test-Revised (Brandt, 1991).

Depressed subjects had a 2-week, single-blind, placebo, drug-wash-out phase at the end of which they had an MRI scan. Subjects who still met DMS-IV criteria for major depression and had HDRS≥18 received controlled treatment with escitalopram for 12 weeks. The starting dose was 10 mg daily for one week and increased to 20 mg daily thereafter for a total of 12 weeks. The dose was reduced to 10 mg daily in those who could not tolerate 20 mg. Subjects received their medication in one-week supply blisters. No subject received psychotherapy.

Depressed subjects had follow-up assessments at 1, 2, 3, 4, 6, 8, 10, and 12 weeks after initiation of escitalopram. Follow-up meetings consisted of a rating session with a research assistant followed by a brief session with a research psychiatrist. Research assistants administered the MADRS, obtained vital signs, questioned the subjects about medication adherence and inspected the escitalopram blister package. The AES and the FrSBe were administered at the last assessment session prior to exiting the study.

MRI

MRI Data Acquisition—MRI scans were acquired on a 1.5T Siemens Vision MR system at the Center for Advanced Brain Imaging (CABI) of the Nathan Kline Institute. Data were processed and analyzed at the Weill-Cornell Brain Imaging Analysis Laboratory. Anatomic imaging included a turbo dual echo scan and high-resolution whole brain images acquired using a 3D T1-weighted MPRAGE for coregistration with fMRI data. fMRI data were acquired using BOLD contrasts in a single-shot multi-slice echo planar image (EPI; TR = 2000 ms, a TE = 50 ms, flip-angle = 90 degrees, matrix=64×64, FOV = 224mm, 22 5mm slices, no gap), which allowed whole brain coverage.

Image Processing—Resting state (awake, closed eyes) data were processed following the procedure of Biswal et al.(Biswal et al.) To eliminate T1 relaxation effects, the first 10 images were discarded. Images were then motion corrected and time shifted using AFNI(Cox, 1996). Next, time series were smoothed using a 6-mm full width-half maximum (FWHM) Gaussian kernel, temporally filtered, and normalized to Montreal Neurological Institute (MNI)152 stereotaxic space ($1 \times 1 \times 1$ mm^3 resolution using FSL; http://www.fmrib.ox.ac.uk/fsl).

MPRAGE scans were segmented using FSL's FAST software, and these segmentations were normalized to MNI152 space using the transformations for the MPRAGE. The gray matter, cerebrospinal fluid (CSF), and total brain signal time series were then extracted using masks derived from the MPRAGE segmentation. These time series, along with the time series for the 6 motion parameters were subsequently used as covariates in a general linear model. In first level analyses, these time series were residualized from the preprocessed resting state data.

FC analysis—To calculate timeseries for each participant we used FMRIB's Linear Image Registration Tool (FLIRT) program to transform each subject's residualized resting-state data into MNI152 space using a 12 DOF linear affine transformation. Next, we calculated the spatial mean time series for each seed ROI. Using the locations described by Fox et al., (Fox et al., 2005) to identify FC within the DMN, one seed was placed in the posterior cingulate cortex (PCC -5, -49, 40). Based on the literature (Sheline et al., 2010a) and regions we observed to be hypoactive in elderly depressed patients during a cognitive control task, to identify FC within the CCN, one seed was placed in each hemisphere in the dorsal ACC (−4/4, 30, 22) and the DLPFC (−36/36, 28, 34). Each seed was spherical in shape with a diameter of 8 mm.

For each seed, individual participant analyses was carried out with GLM of FSL's FEAT toolbox using seed-based regression approaches on the residualized resting state data (Biswal et al., Hoptman et al.). The timeseries for each seed was entered as a predictor. Individual subject-level, Z-statistic images were generated for each seed.

Data Analysis

Initially, Mann-Whitney and chi-square tests were used to identify demographic and clinical variables distinguishing depressed from normal subjects and depressed subjects who achieved remission from those who remained symptomatic. Group level analyses of FC were conducted using FLAME (FMRIB's Local Analysis of Mixed Effects), to produce thresholded z-score maps of activity associated with each seed. Images were thresholded using clusters determined by $z > 2.3$ and a corrected cluster significance threshold of $p < 0.05$ (Worsley et al., 1992). These maps revealed networks for each group (depressed patients, controls, remitters, nonremitters), as well as group difference maps for direct group comparisons (e.g., patients vs. controls, remitters vs. nonremitters). Partial correlations with age as covariate were used to study the association of FC networks with clinical characteristics at baseline. The relationship of FC within CCN and DMN at baseline to the course of depressive symptoms and signs during the 12 weeks of treatment was studied with mixed effects models. Survival analysis was used to study the relationship of resting FC within the CCN and DMN to time to remission. For clinical variables assessed at baseline and at study exit (apathy, dysexecutive behavior), regression was used to study the relationships of FC to the values of these clinical variables at the end of treatment. Two tailed significance tests were used in all comparisons.

RESULTS

Subjects

Twenty-six older adults were studied. Of these, 16 were non-demented, non-MCI subjects (mean: 69 years, SD: 5.5) with non-psychotic, unipolar major depression (baseline MADRS mean: 23.5, SD: 4.0) and 10 were normal subjects (mean age: 68.6 years, SD: 7.0). There were no differences in education (years), overall cognitive impairment (MMSE, DRS), memory (HVLT), and response inhibition (Stroop Color-Word) between depressed and normal subjects. However, depressed subjects had a higher depression (MADRS: z=4.2,

p<0.0001) and disability (WHODAS: z=3.7, p<0.0001) scores than normal subjects. The depressed group was divided into remitters (MADRS ≤7 for two consecutive weeks) and non-remitters. There were no demographic or clinical differences between remitters and non-remitters at baseline with the exception of response inhibition in which non-remitters had more abnormal scores (Table 1).

Depressed subjects were scanned at the end of a 2-week single-blind placebo phase. Then, they received escitalopram at mean dose of 16.25 mg (SD: 5.0, range 10–20) daily for 12 weeks. Non-depressed subjects were scanned at study entry.

Baseline FC at Rest in Depressed Elders and Controls

Cognitive Control Network (CCN)—Both non-depressed and depressed subjects showed significant FC within a network that included the dorsal ACC, DLPFC, supramarginal. superior parietal and inferior parietal regions, and thalamus (See Figures 1a and 1b for non-depressed and depressed, respectively). Relative to depressed subjects, when a seed was placed in the left dorsal ACC, non-depressed subjects had greater FC in the left DLPFC (BA 9; MNI coordinates x =−24, y=40, z=32) (Figure 1c). When a seed was placed in the left DLPFC, relative to depressed patients, non-depressed subjects demonstrated greater FC in the bilateral inferior parietal cortices (BA 40; MNI coordinates x = 54/− 54, y= −44, z=36). No significant group differences were observed when the seed was placed either in the right DLPFC or the right ACC. Depressed subjects had no regions of greater FC than normal subjects with either the dorsal ACC or LPFC seeds.

In the depressed group, partial correlation with age as covariate showed that FC within the CCN was associated with baseline Stroop Color Word scores (r=0.34, df=13, p=0.21), but this relationship did not reach significance. There was no association between FC of the CCN and Stroop Color Word in normal subjects (r=0.06), perhaps because of limited variability in Stroop values.

Default Mode Network (DMN)—Both depressed and normal subjects demonstrated significant FC within a network that included the posterior cingulate/precuneus, portions of the VMPFC, lateral parietal regions, perigenual ACC, DMPFC, and medial temporal regions (Figure 2a and 2b). Relative to non-depressed subjects, depressed subjects had greater FC in the left precuneus (BA 7; MNI coordinates x = −6, −70, 62), the subgenual ACC (BAs 25/32 MNI coordinates x = −4, 26, −10), the VMPFC (BA 11; MNI coordinates x = −4, 36, −16), and lateral parietal regions (Figure 2c).

In the depressed group, partial correlation with age as the covariate showed that DMN FC (r=0.55, df=14, p=0.034) was associated with pessimism (MADRS item 9) at baseline. Age was not significantly correlated with pessimism. There was no significant association between DMN FC and overall severity of depression (MADRS).

Baseline CCN and DMN FC at Rest and the Course of Depression

Next we compared, FC in patients who remitted following treatment versus patients who remained symptomatic (Remitters, NonRemitters). Remission was defined as MADRS≤7 for two consecutive weeks and absence of DSM-IV diagnosis of depression. Seeds placed in the dorsal ACC, did not result in any significant group differences. A seed placed in the left DLPFC yielded greater FC in the bilateral dorsal ACC (BAs 24/32; MNI coordinates x= 4, y =34, z = 22, right DLPFC (BA 10; MNI coordinates x=44, y=46, z=12), and bilateral inferior parietal cortices (BA 40; MNI coordinates x= 38/−38, y =−56, z=52) in Remitters (Figure 3). When the seed was placed in the right DLPFC Remitters had greater FC than Non-Remitters in the right inferior parietal region (BA 40; MNI coordinates x= 38, y =−56,

z=52). Non-Remitters did not exhibit any areas of greater FC. Analyses of the default network did not yield any significant group differences between Remitters and Non-Remitters.

Next, in the depressed group, we used mixed effects models to study the relationship of FC within CCN and DMN at baseline and the course of depression (MADRS) over the 12 weeks of escitalopram treatment. Age was used as a covariate. A model consisting of baseline resting FC in CCN, DMN FC, age, and time was associated with change in MADRS during the 12 week treatment phase (χ^2= 61.15, p<0.0001). Baseline CCN FC predicted decline of MADRS (β= −18.19, SE= 5.3, t(89)= −3.42, p<0.001). Neither DMN FC (p=0.72) nor age (p=0.40) were significantly associated with the course of MADRS.

We used survival analysis to study the relationship of a model consisting of CCN and DMN resting FC to remission rates (MADRS≤7 for 2 consecutive weeks) during escitalopram treatment. The overall model was associated with remission (Wald χ^2=13.51, df=2, p<0.001). However, only CCN FC had a significant relationship with remission (Wald χ^2: 9.5, df:1, p<0.002); low FC predicted non-remission. DMN FC was not associated with remission (Wald χ^2=0.48, df=1, p=0.49). Depressed subjects who achieved remission had received similar dosages of escitalopram to those who did not meet criteria for remission. Three remitters received 10 mg of escitalopram daily and five received 20 mg. The corresponding numbers for non-remitters were four and four.

Baseline Resting FC in CCN and DMN, Apathy, and Dysexecutive Behavior at 12 Weeks—In the depressed group, apathy (AES) and dysexecutive behavior (FrSBe) were assessed at baseline and after 12 weeks of escitalopram treatment. A regression model was constructed to assess the relationship of baseline resting FC at CCN to apathy (AES) after 12 weeks of treatment with escitalopram. Baseline AES and age were used as covariates. The overall model was significant ($F_{(3,11)=}$6.30, p=0.0095). Baseline CCN FC (β:-26.60, SE: 11.06, p<0.035) was associated with AES at 12 weeks (Figure 4a), while age and baseline AES had no significant association.

A similar analysis assessed the relationship of baseline FC within the CCN to dysexecutive behavior (FrSBe) after 12 weeks of escitalopram treatment. The overall model was significant ($F_{(3,11)}$=15.1, p=0.0003). Baseline CCN FC (β=−31.28, SE=9.61, p<0.008) was associated with FrSBe at 12 weeks (Figure 4b), while age and baseline FrSBe had no significant association. Baseline FC within the DMN was not associated with either apathy or dysexecutive behavior at 12 weeks.

DISCUSSION

The principal finding of this study is that low resting FC within the CCN and high FC within the DMN characterize late-life depression. Beyond this “double dissociation” distinguishing depressed from normal older adults, resting FC at the CCN and the DMN were related to distinct clinical characteristics. Resting FC at the CCN during the depressive episode predicted poor remission rate after treatment with escitalopram and persistence of depression, apathy and dysexecutive behavior at the end of treatment. In contrast, resting FC of the DMN was correlated with pessimism during the depressive episode but was not associated with treatment response.

To our knowledge this is the first study to identify an imbalance of resting FC within the CCN and DMN in late-life depression and demonstrate a relationship between FC within CCN and poor outcomes of depression. These findings should be viewed in the context of the study’s limitations. These include the small number of subjects, the use of an 1.5 T

scanner, and the absence of a placebo control group. Use of a higher field scanner may have revealed additional abnormalities. Placebo response is imbedded in escitalopram response, although the placebo effect is reduced by our placebo lead-in. A placebo control group may have allowed to distinguish escitalopram from placebo response. Nonetheless, focusing on overall response (drug + placebo) may be appropriate for the first study of its kind. A potential advantage of a non-placebo controlled study is low selection bias since placebo controlled studies tend to recruit “less sick” patients (Roose et al., 2004).

Low FC within the CCN is consistent both with the clinical presentation and with available neuroimaging findings in late-life depression. A cardinal feature of major depression is difficulty engaging in goal-directed behavior while ignoring irrelevant, mainly negatively-valenced, stimuli. These functions rely on the CCN, which enables individuals to flexibly adapt information processing to changing demands and is a central aspect of several functions, including attention allocation, working memory and cognitive inhibition (Carter and van Veen, 2007, Miller and Cohen, 2001). Moreover, the CCN influences emotional associations by biasing processing either in affective networks or in perceptual and associative memory systems (Davidson et al., 2002) and influences underdetermined responding (Barch et al., 2000), emotion regulation in anxiety (Bishop et al., 2004), and thought suppression (Anderson et al., 2004). PET and fMRI studies have shown decreased metabolic activity in dACC and DLPFC during depression (Aizenstein et al., 2009, Drevets et al., 1997, Mayberg et al., 1999). Depressed patients have decreased DLPFC activity in response to cognitive control tasks and sustained amygdala reactivity during emotional tasks (Siegle et al., 2007). Hypoactivity of the DLPFC following challenge has been documented during depression in elderly patients (Aizenstein et al., 2009). Consistent with our findings, depressed elderly patients have low FC between the DLPFC and dACC during a cognitive conflict task, which persisted after antidepressant treatment (Aizenstein et al., 2009).

The relationship of low resting FC within CCN to poor remission rate and persistence of depressive symptoms, apathy and dysexecutive behavior is consistent with earlier findings suggesting that CCN abnormalities influence response to antidepressants. Abnormal response inhibition, working memory, and processing speed, characterize depressed elderly non-remitters or predict long time to remission (Sheline et al., 2010b, Alexopoulos et al., 2005, Alexopoulos et al., 2004, Kalayam and Alexopoulos, 1999). Microstructural white matter abnormalities in the cognitive control territory have been associated with executive dysfunction (Murphy et al., 2007) and poor response to escitalopram (Alexopoulos et al., 2010, Alexopoulos et al., 2008, Alexopoulos et al., 2002), although some disagreement exists(Taylor et al., 2008). These abnormalities may disrupt the communication of the CCN with ventral limbic regions, thus interfering with normalization of their functions and inhibiting remission of depression (Alexopoulos et al., 2008). Indeed, increased activation in DLPFC, ACC and limbic regions during a task of inhibitory control was shown to predict the extent of response to escitalopram (Langenecker et al., 2007). Other studies of adults observed that remission of depression is associated with metabolic changes, mainly increases, in dACC (BA 24b), DLPFC (BA 46/9), and inferior parietal lobe (BA 40) (Drevets, 2000, Fitzgerald et al., 2006, Mayberg et al., 1997). The persistence of apathy and dysexecutive behavior is consistent with findings suggesting that low FC between the DLPFC and the dACC remains after antidepressant treatment(Aizenstein et al., 2009). Frontal lobe syndromes often include apathy and dysexecutive behaviors, including inability to plan, sequence, initiate and flexibly adjust behavior to task-related demands(Lezak et al., 2004), symptoms that often persist after improvement of depression(Royall, 1999).

Increased resting FC within the DMN is consistent with earlier findings in depressed adults (Sheline et al., 2010b) and with what is known about the function of DMN structures. The DMN is thought to mediate self-referential thinking, including the development of a

personal perspective by taking into consideration the past and planning for the future and by evaluating beliefs and intentions of others(Buckner et al., 2008, Raichle et al., 2001, Raichle and Snyder, 2007, Sheline et al., 2009). Self-referential thinking is often impaired in depression and leads to a negativity bias (Herwig et al.), most pronounced during depressive episodes. Recently, it was shown that the CCN, the DMN, and other affective networks have increased resting FC with the same bilateral DMPFC region (dorsal nexus)(Sheline et al., 2010b). Further the dorsal nexus has increased FC at rest in depressed adults compared to controls. Increased FC in this region may explain the concurrent occurrence of heterogeneous symptoms in depression.

Increased FC in portions of the DMN during the depressed state in the older adults is also consistent with a recent report of increased DMN FC in the dorsomedial PFC and orbitofrontal cortex in elderly depressed patients prior to treatment (Wu et al., 2011). Some of the abnormalities in DMN FC improved with antidepressant treatment (Wu et al., 2011). Further, FC of DMN and other networks involved in emotional regulation are related to WMH burden (Wu et al., 2011) and microstructural white matter indices as measured by tractography (Steffens et al., 2011).

In conclusion, we observed that low resting FC within the CCN distinguishes depressed from normal older adults and predicts persistence of depressive symptoms and signs, low remission rate, apathy and dysexecutive behavior. In contrast, resting FC within the DMN is increased in late-life depression and correlated with pessimism but does not predict treatment response. If confirmed, these findings may serve as a signature of the brain's functional topography characterizing late-life depression and sustaining its symptoms. By identifying the network abnormalities underlying biologically meaningful characteristics (apathy, dysexecutive behavior, pessimism) and sustaining late-life depression, these findings can provide a novel target on which new somatic and psychosocial treatments can be tested.

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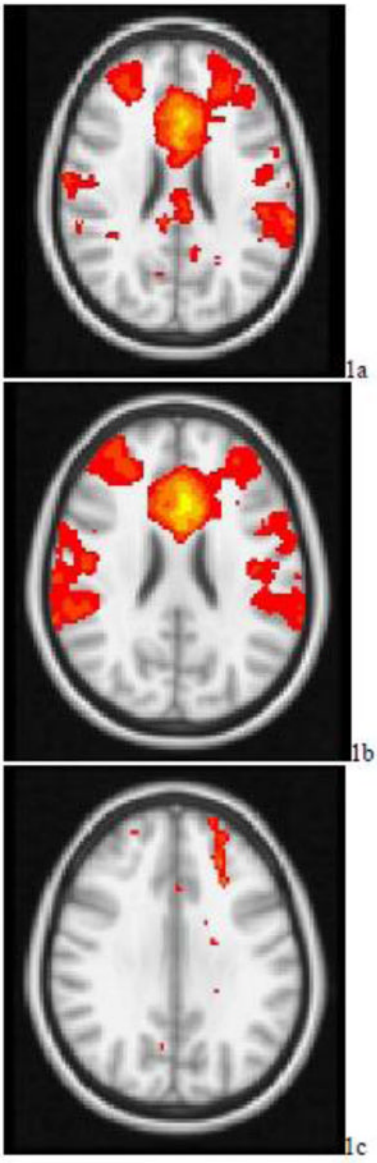


Figure 1.
t-maps of the resting state connectivity of the cognitive control network for a) the non-depressed elderly; b) elderly depressed patients; c) non-depressed elderly > elderly depressed patients. Images were thresholded using clusters determined by $z > 2.3$ and a corrected cluster significance threshold of $p < 0.05$.

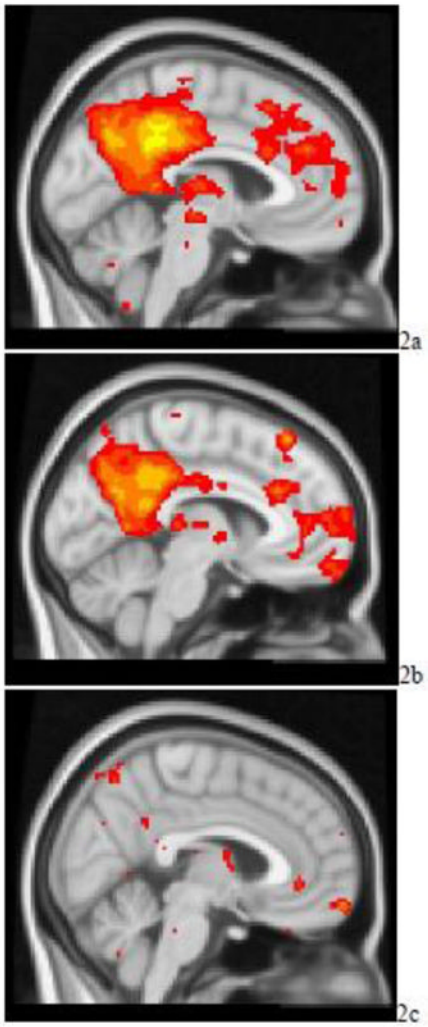


Figure 2.

t-maps of the resting state connectivity of the default mode network for a) the non-depressed elderly subjects; b) elderly depressed patients; c) elderly depressed patients > non-depressed elderly subjects. Images were thresholded using clusters determined by $z > 2.3$ and a corrected cluster significance threshold of $p < 0.05$.

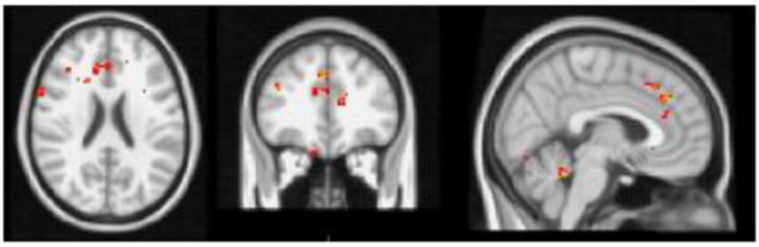
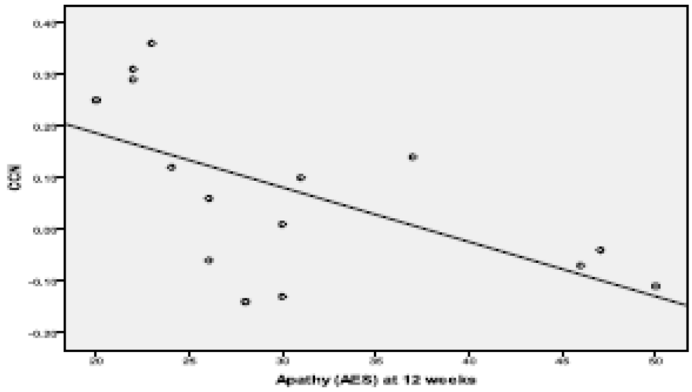


Figure 3.
t-maps of the resting state connectivity of the cognitive control network for Remitters > NonRemitters. Images were thresholded using clusters determined by $z > 2.3$ and a corrected cluster significance threshold of $p < 0.05$.

a)



b)

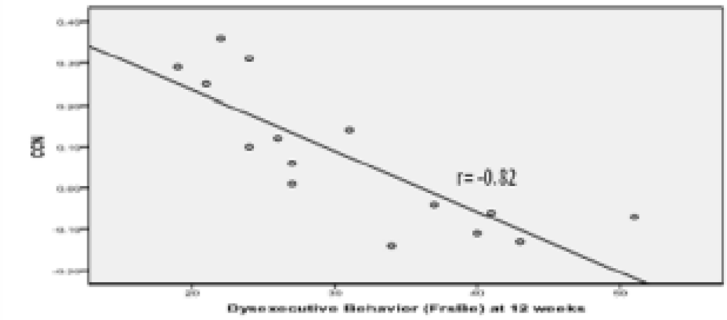


Figure 4.

a) Relationship between Apathy (AES) at 12 Weeks and Baseline Cognitive Control Network FC in Depressed Older Adults. b) Relationship between Dysexecutive Behavior (FrsBe) at week 12 and baseline Cognitive Control Network FC in Depressed Older Adults.

Table 1

Characteristics of Remitted and Non- Remitted Depressed Patients and Non-depressed Comparison Subjects at Baseline

Variable	Remitted (N=16)	Non-Remitted (N=16)	Non-Depressed (N=10)
	Mean (SD)	Mean (SD)	Mean (SD)
Age	67.9 (4.7)	70.1 (6.3)	68.6 (7.0)
Education	16.5 (1.4)	17.9 (2.9)	16.3 (3.8)
Ham-D[1]	24.9 (4.1)	26.3 (3.7)	2.4 (1.8)
MADRS[2]	22.3 (2.6)	24.8 (5.0)	2.1 (1.3)
MiniMental State Exam	29.1 (1.1)	29.1 (0.6)	28.5 (0.97)
DRS[3]Total	137.8 (3.0)	135.3 (5.4)	137.3 (3.9)
DRS Initiation/Perseveration	35.8 (0.71)	34.4 (4.3)	35.9 (1.1)
Stroop Color Word	40.3 (7.2)	30.4 (9.4)*	38.5 (6.8)
FrSBe[4]	34.6 (7.4)	40.8 (4.7)	--
Apathy Evaluation Scale	32.8 (6.9)	39.3 (8.6)	--
Trails B	77.7 (19.5)	98.4 (39.4)	75.7 (25.3)
Trails A	36.8 (11.0)	34.4 (7.2)	30.0 (11.1)
HVLT-R[5]Immediate Recall	26.5 (4.2)	27.5 (5.3)	25.5 (5.1)
HVLT-R Delayed Recall	8.4 (2.4)	9.9 (1.6)	9.5 (2.2)

[1]24-item Hamilton Depression Rating Scale;

[2]Montgomery Asberg Depression Rating Scale;

[3]Dementia Rating Scale;

[4]Frontal Systems Behavior Rating Scale

[5]Hopkins Verbal Learning Test- Revised

*Comparison between Remitters and Non-Remitters was significantly different Mann Whitney U=51, z=2.0, p=0.045. No other comparisons between Remitters and Non-Remitters achieved statistical significance.