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Preliminary communication

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 characterizes late-life depression and predicts 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 time series 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 FC within the CCN and high resting FC within the DMN distinguished depressed from normal elderly subjects. Beyond this "double dissociation", low resting 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 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 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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1. 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 (Aizenstein et al., 2009; Drevets et al., 1997; Mayberg et al., 1999). 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

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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 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 (Biswal et al., 1995; Cordes et al., 2000, 2001; De Luca et al., 2005; Fox and Raichle, 2007; Fox et al., 2006, 2009; 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 and Padmala, 2005; Pessoa et al., 2002; Ress and Heeger, 2003; Ress et al., 2000; 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 resting state 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).

2. Methods

2.1. 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 the Nathan Kline Institute.