The Structural and Functional Neuroanatomy of Post-Stroke Depression and Executive Dysfunction: A Review of Neuroimaging Findings and Implications for Treatment

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Abstract

Post-stroke depression and executive dysfunction co-occur and are highly debilitating. Few treatments alleviate both depression and executive dysfunction after stroke. Understanding the brain network changes underlying post-stroke depression with executive dysfunction can inform the development of targeted and efficacious treatment. In this review, we synthesize neuroimaging findings in post-stroke depression and post-stroke executive dysfunction and highlight the network commonalities that may underlie this comorbidity. Structural and functional alterations in the cognitive control network, salience network, and default mode network are associated with depression and executive dysfunction after stroke. Specifically, post-stroke depression and executive dysfunction are both linked to changes in intrinsic functional connectivity within resting state networks, functional over-connectivity between the default mode and salience/cognitive control networks, and reduced cross-hemispheric fronto-parietal functional connectivity. Cognitive training and noninvasive brain stimulation targeted at these brain network abnormalities and specific clinical phenotypes may help advance treatment for post-stroke depression with executive dysfunction.

Keywords

cerebrovascular disease, neuroimaging, magnetic resonance imaging, cognitive control, default mode network

Introduction

Post-stroke depression (PSD) and executive dysfunction affect a large percentage of stroke survivors and are independently associated with short-term and long-term disability and poor quality of life.1-7 Executive functions refer to a set of heterogenous cognitive abilities that enable goal-directed behavior and include planning, organization, initiation, working memory, inhibition of task-irrelevant information, shifting, and cognitive flexibility.8,9 The clinical expression of executive dysfunction can include symptoms of apathy, impulsivity, and behavioral dysregulation and result in loss of independence in daily functioning.10 Two weeks post-stroke, 86% of stroke patients with depression exhibit cognitive dysfunction compared to non-depressed patients who have a rate of cognitive dysfunction of 61%.11 Approximately 23% of stroke patients experience depression with executive dysfunction at 1 month and 3 months post-stroke,12 the majority of whom continue to experience both depression and executive dysfunction at 2 years.12 Stroke patients with executive dysfunction report more severe depressive symptoms,14 poorer psychosocial functioning, less independence in activities of daily living,15 and poorer community participation and reintegration.16 Depression and executive dysfunction is associated with shorter time to stroke recurrence17 and death.18

Few efficacious treatments exist for this debilitating comorbidity. Selective serotonin reuptake inhibitors alleviate depression symptoms in PSD but do not typically improve cognition or functional outcome.19,20 Evidence for medication-induced cognitive improvement in the setting of PSD is scant for any of the monoamines.21 This is consistent with the finding that executive dysfunction confers non-response to antidepressant treatment in late-life depression.22,23 While methylphenidate can improve working memory after stroke, it does not alleviate depression.24 Repetitive transcranial magnetic stimulation
(rTMS) delivered to the standard therapeutic target of the left
dorsolateral prefrontal cortex improves depression symptoms
but to date the impact on comorbid executive functioning35 is
limited. Thus, stroke patients with comorbid depression and
effective and efficient treatments.

diseases without adequate existing treatment options.

A better understanding of the brain network changes under-
lying post-stroke depression with executive dysfunction can
both elucidate the brain mechanisms of this comorbidity and
inform the development of targeted and efficacious interven-
tions. In this review, we synthesize and integrate the results of
studies that have (often separately) examined the brain-based
mechanisms of depression and executive dysfunction post-
stroke. We searched for the following title and abstract key-
words in the National Library of Medicine database (PubMed)
with a focus on studies published in the past 10 years:
“post-stroke depression,” “stroke,” “executive [dys]function,”
“cognition,” “neuroimaging,” “MRI.” We further surveyed the
references cited of individual articles to capture additional
studies. We included studies that defined cognitive functioning
broadly as long as results were reported for a measure of exec-
utive functioning, and we excluded studies of patients with
dementia. Our review highlights overlapping network involve-
ment as well as brain network features that may be more unique
to post-stroke depression and post-stroke executive dysfunc-
tion, respectively. We focus primarily on neuroimaging studies
that have taken a network-based approach to shedding light on
post-stroke structural and functional network connectivity
abnormalities. We then discuss possible treatments that can
target the circuitry underlying the comorbidity. We argue that
a brain-based conceptualization and model of post-stroke
depression with executive dysfunction is needed to develop
effective and efficient treatments.

Networks Central to Post-Stroke Depression and
Executive Dysfunction

As will be discussed below, the cognitive control network,
default mode network, and salience network are relevant to
depression and executive dysfunction after stroke. Definitions
of these networks vary, but for the purpose of this review we
define networks as follows. The cognitive control network—
often referred to as the frontoparietal or executive control
network—encompasses the dorsolateral prefrontal cortex and
posterior parietal cortex26,27 and flexibly directs attentional
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Functional Alterations

Strokes precipitate abnormal intrinsic functional connectivity in networks supporting the experience and regulation of emotions, notably the cognitive control network. Weaker resting state functional connectivity (rsFC) between the dorsolateral prefrontal cortex and the supramarginal gyrus—two key regions of the cognitive control network—is associated with depression severity.52 Nodes within the cognitive control network have diminished degree centrality (decreased importance of the dorsolateral prefrontal cortex) to the organization of the functional connectome in PSD.53 This weakening of connectivity within the cognitive control network parallels that seen in major depression and may relate to difficulty in engaging in adaptive control strategies to regulate mood after a stroke.

Heightened anterior default mode network activity is often observed in non-stroke patients with major depressive disorder and a similar pattern has been observed in PSD. Though in PSD, there is increased rsFC in more posterior nodes of the default mode network, including the left inferior parietal cortex, left middle temporal cortex, and left precuneus.54,55 The regional homogeneity—or synchronization of local functional connections within a region—is also increased within the posterior default mode network in PSD.56

The optimal balance between network segregation and integration appears to be one in which networks act as “modules” with high connectivity within networks and relatively sparser connectivity between networks.57 This modular network architecture normally promotes efficient information processing. In PSD, increased functional connectivity between networks that are typically segregated (the default mode network and cognitive control network) may result in a loss of modularity and optimal network efficiency and contribute to the subsequent manifestation of PSD symptoms. After stroke, greater depression severity is associated with increased rsFC between the default mode network and salience network and between the salience network and ventral limbic regions such as the amygdala.39 These findings suggest the possibility of a pathological “over-connectivity” between the salience network and networks that are typically functionally segregated (default mode network, limbic regions). The anterior cingulate cortex and insula both exhibit greater degree centrality (relative importance in a network) in PSD, further highlighting the role of the salience network in PSD.53

Post-Stroke Executive Dysfunction

Structural Alterations

Frontal, parietal, and subcortical lesions after a stroke are associated with executive dysfunction59 via disconnection of cognitive control and salience networks as well as subcortical regions. Dysconnectivity can be determined by overlaying a mask of a patient’s stroke lesion onto normative (control) tractograms, to calculate the amount of inferred disconnection in specific regions. Such lesion-related structural disconnection in the left and right superior and inferior frontal-parietal region, angular gyrus, putamen, and globus pallidus are associated with inattention and executive dysfunction60 and contribute to loss of independence in daily functioning at 6 months post-stroke.61

Measures of microstructural connectivity using diffusion tensor imaging also implicates cognitive control, salience, and subcortical regions. Poor verbal fluency—a measure of initiative, sustained attention, and flexible thinking—is associated with loss of white matter integrity in the arcuate fasciculus, uncinate fasciculus, and cortico-subcortical pathways that result in disconnection of the anterior cingulate cortex, mid-cingulate cortex, middle and inferior frontal gyrus, striatum, and thalamus.52 These structural disconnections are also related to lower intrinsic functional connectivity in the cognitive control (frontoparietal) network and lower functional connectivity between the mid-cingulate and the thalamus and striatum.52

Functional Connectivity

Using standard clinical CT and MR imaging, stroke lesions can also be overlayed on normative functional connectomes to determine functional network disconnection.63,64 Stroke lesions that disrupt intrinsic functional connectivity to the supramarginal gyrus and insula are associated with impaired decision-making.65 The supramarginal gyrus is a key node of the cognitive control network while the insula is a node in the salience network.66 The insula has also been implicated in post-stroke affective dysfunction55 and may represent one shared neuroanatomical substrate common between both PSD and post-stroke executive dysfunction.

Resting state FC within the cognitive control network, salience network, and default mode network is implicated in executive dysfunction after stroke. Following stroke, more efficient multitasking is associated with greater rsFC in the cognitive control network.57 Greater local, within-network rsFC in the anterior cingulate cortex is linked to better divided attention and working memory.68 Increased intrinsic functional activity in the default mode network is associated with better verbal fluency69 and rsFC coherence in the posterior cingulate and precuneus correlates with better performance on a measure of auditory attention.68 Thus, greater within-network (intrinsic) connectivity in cognitive control, salience, and default mode networks appears to be consistently associated with stronger attention and executive function after stroke.

Just as in PSD, increased rsFC between networks is associated with executive dysfunction. Attention/working memory dysfunction is associated with increased connectivity between the default mode network and cortical attention network, and between the default mode network and the cingulo-opercular task control (salience) network.70 Worse attention and working memory are also associated with lower cross-hemispheric intrinsic functional connectivity within frontal and parietal regions of the cognitive control network, paralleling findings in PSD.71 Thus, over-connectivity between functional
networks and disruptions to cross-hemispheric integration may be common factors underlying PSD and executive dysfunction.

### Post-Stroke Depression With Executive Dysfunction

Despite the additive burden of post-stroke depression coupled with executive dysfunction, there are only a few studies that have directly investigated the neuroanatomical correlates and mechanisms in patients with both depression and executive dysfunction. Stroke patients who are both depressed and have executive dysfunction have greater structural atrophy to frontal and subcortical regions from the infarct compared to patients with only depression or with neither depression nor executive dysfunction.\(^{15}\) Worse white matter integrity in frontal and parietal regions, as assessed via diffusion tensor imaging, is linked to both depression symptoms and executive dysfunction in the same sample of subacute stroke patients.\(^{72}\)

Synthesis of findings from studies that have investigated depression and executive dysfunction separately suggest specific resting state network commonalities and are useful for generating testable hypotheses in future studies (summarized in Table 1 and Figure 1). Connectivity between the default mode, cognitive control, and salience networks may be common substrates underlying post-stroke depression and executive dysfunction. Both depression and executive dysfunction are associated with increased functional connectivity between the default mode network and cognitive control network. This increased between-network connectivity may reflect an abnormal loss in the modular architecture of brain networks that is thought to be adaptive for healthy cognitive and emotional functioning. Loss of cross-hemispheric integration also appears to be common to executive dysfunction and depression.

<table>
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<tr>
<th>Table 1. Summary of Structural and Functional Network Changes in Post-Stroke Depression and Post-Stroke Executive Dysfunction.</th>
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<tr>
<td><strong>Post-stroke depression</strong></td>
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<tr>
<td><strong>Structural Connectivity</strong></td>
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<tr>
<td>superior/middle frontal connectivity</td>
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<td>frontostriatal connectivity</td>
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<td>frontolimbic connectivity</td>
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<td><strong>Intrinsic (within-network) functional connectivity</strong></td>
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<td>Cognitive Control Network</td>
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<td>posterior Default Mode Network</td>
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<td><strong>Extrinsic (between-network) functional connectivity</strong></td>
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<td>Default Mode Network-Salience Network</td>
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<td>Salience Network-Ventral Limbic Regions</td>
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<td><strong>Cross-hemispheric functional connectivity</strong></td>
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Figure 1. Visual depiction of intrinsic (within-network) functional connectivity changes underlying post-stroke depression (a) and post-stroke executive dysfunction (b). Spheres represent network nodes based on the Power et al\(^ {73}\) functional parcellation. DMN = default mode network; SAL = salience network (salience and cingulo-opercular task control networks from Power et al\(^ {73}\)), CCN = cognitive control network (frontoparietal network from Power et al\(^ {15}\)). Note that this figure is a schematic representation of our literature synthesis and does not represent actual data on functional activation.
Finally, also observed is a reduction in intrinsic functional connectivity within the cognitive control network.

Intrinsic functional connectivity within posterior nodes of the default mode network may be elements of this circuitry that diverges between depression and executive dysfunction. In studies investigating PSD alone, depression symptoms are typically associated with an increase in rsFC within the posterior cingulate and precuneus. In contrast, post-stroke executive dysfunction is associated with decreased rsFC in the posterior cingulate. Because these findings have come from separate samples investigating executive dysfunction or depression separately, clarifying the role of the posterior default mode network requires further study in a sample of patients with depression and executive dysfunction.

**Implications for Treating Post-Stroke Depression With Executive Dysfunction**

The common and divergent neural underpinnings of post-stroke depression and executive dysfunction can help refine and improve existing treatment by targeting network abnormalities in the cognitive control network, salience network, and default mode network. Stroke patients whose cognitive impairment improves in the first year after stroke exhibit an increase in modular network organization, i.e. a return to the adaptive segregation, between the default mode network and cognitive control network, which highlights the importance of network re-organization in recovery. Recovery from PSD may also be due in part to structural changes in the posterior cingulate cortex.

Cognitive remediation could alleviate both depression and executive dysfunction via targeting of, and change in, rsFC in the cognitive control network and default mode network. In older adults with depression, computerized cognitive training targeting the cognitive control network is associated with improvements in both depression and executive functions. A group-based metacognitive intervention for older adults that focused on learning executive functioning strategies was associated with increased rsFC within the cognitive control network, as well as increased anticorrelation between the cognitive control network and default mode network. A cognitive intervention designed to improve reasoning and problem-solving in aging adults similarly found increased cerebral blood flow in regions of the cognitive control network post-training. These 2 studies did not investigate depression or mood symptoms as an outcome, however. Examining the efficacy of computerized cognitive training and cognitive strategy training that targets the cognitive control and salience networks in PSD with executive dysfunction may help to both identify efficacious treatment approaches and the further elucidate underlying mechanisms.

The efficacy of noninvasive brain stimulation for depression and executive dysfunction may be improved with targeting of different sites that underlie both depression and executive dysfunction, such as the salience network and parietal regions of the cognitive control network. Deep TMS enables stimulation below the cortical surface, such as to the anterior cingulate and insula, and has been applied to late-life depression. Although a recent trial evaluating deep TMS to the salience network (anterior cingulate cortex, insula) in treating central pain after stroke did not demonstrate effects on mood symptoms or cognitive function, patients were included only if they had pain syndromes and those with psychiatric/cognitive disorders such as PSD and executive dysfunction were excluded.

Use of resting state fMRI can improve targeting and efficacy of treatment for major depression and such an approach could be applied to PSD with executive dysfunction. The dorsomedial prefrontal cortex, part of the anterior default mode network, has emerged as an alternate stimulation site in depression and psychiatric disorders, though given that the connectivity of the default mode network may differ in depression versus executive dysfunction after stroke, it is unclear whether stimulation of this alternate site may produce gains in both depression and executive dysfunction after stroke.

Targeting of specific clinical and cognitive phenotypes may also enhance the efficacy of interventions for post-stroke depression with executive dysfunction. In patients with PSD, specific symptoms are related to specific cognitive difficulties. That is, in patients with PSD, the severity of apathy symptoms ("lassitude" and "inability to feel") is related to executive dysfunction, while the severity of sadness and distress/anxiety-based symptoms is not correlated with executive dysfunction. Although this study did not use neuroimaging, the findings suggest that depressed patients post-stroke who experience apathy may be especially vulnerable to executive dysfunction and compromise in the salience network and the cognitive control network. Thus, an intervention aimed to target PSD with executive dysfunction may be well-suited to individuals who manifest clinical signs and symptoms of apathy as part of their depressive symptoms. It should be noted that apathy can manifest in the context of PSD and can also occur as a separate neuropsychiatric syndrome with distinct neurobiological features post-stroke such as the location and extent of cerebrovascular pathology.

More generally, a critical approach for future studies is to simultaneously assess structural and functional connectivity in a single sample of patients with depression and executive dysfunction. In stroke patients, structural disconnection between cortical regions is correlated with the magnitude of functional connectivity. Both structural and functional disconnection contribute unique variance to predicting cognitive functioning and in cerebrovascular disease are associated with executive functioning. The possibility that functional connectivity may shift or compensate for structural disconnection over time is also a relevant question to ensure that appropriate treatments are delivered depending on the time period post-stroke, especially as chronic stroke survivors can experience secondary degeneration in the thalamus, amygdala, hippocampus, and cingulum bundle.

A limitation of our review and of the literature is that is that it is often clinically and conceptually difficult to differentiate...
Additional Etiologic Considerations for Post-Stroke Depression With Executive Dysfunction

Though we have focused on the structural and functional networks underlying post-stroke depression and executive dysfunction, there are additional pathophysiological mechanisms that are likely related to the syndrome. Post-stroke executive dysfunction and depression are both related to altered monoamine neurotransmission including disruption to dopaminergic, noradrenergic, and serotonergic pathways. However, similar to MRI studies, studies of neurotransmitter function post-stroke typically examine the relationship of neurotransmission to depression or executive dysfunction, and do not assess both in the same sample of patients. In addition, inflammation and heightened pro-inflammatory cytokines likely contribute to the development of post-stroke depression with executive dysfunction. Within a biopsychosocial framework, the sudden and debilitating alteration in physical function due to stroke, the associated stress of loss of independence, and social and family stressors can also precipitate and perpetuate post-stroke depression. It is possible that a bidirectional relationship exists between neurobiological disruptions and stress post-stroke, such that chronic psychosocial stress experienced after stroke alters functional network organization and contributes to PSD symptoms.

Conclusions

Post-stroke depression with executive dysfunction is common and debilitating. Many existing treatments confer minimal benefit in addressing both depression and executive dysfunction. Treatments can be improved by better targeting of the common neural substrates underlying depression and executive dysfunction after stroke. Both of these comorbid syndromes are associated with altered intrinsic and extrinsic structural and functional connectivity in the cognitive control, salience, and default mode networks, as well as a loss of cross-hemispheric functional connectivity. Use of cognitive training to target the cognitive control and/or salience networks may be fruitful in alleviating depression and executive dysfunction, as has been shown in older adults with depression. Noninvasive brain stimulation is a promising approach, but may require use of novel techniques and targeting of alternate stimulation sites. Tailoring treatments to specific clinical phenotypes such as PSD with prominent apathy symptoms, in which executive dysfunction commonly co-occurs and which presumably implicates the salience and cognitive control networks, can also enhance treatment. More broadly, clinicians and researchers should design neuroimaging studies to further elucidate the neuroimaging markers of depression and executive dysfunction in the same sample of patients. The ultimate goal of this line of research is to improve functional outcomes after stroke, and measures of disability and function should also be included as outcome variables in treatment trials.

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