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Review Article

# Pathoconnectomics of cognitive impairment in small vessel disease: A systematic review

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**Abstract**

**Introduction:** Cerebral small vessel disease (CSVD) is a highly prevalent condition associated with diffuse ischemic damage and cognitive dysfunction particularly in executive function and attention. Functional brain imaging studies can reveal mechanisms of cognitive impairment in CSVD, although findings are mixed.

**Methods:** A systematic review integrating findings from functional magnetic resonance imaging and electroencephalography in CSVD is involved.

**Results:** CSVD damages long-range white matter tracts connecting nodes within distributed brain networks. It also disrupts frontosubcortical circuits and cholinergic fiber tracts mediating attentional processes. These changes, illustrated within a model of network dynamics, synergistically relate to neurodegenerative pathology contributing to dementia.

**Discussion:** The effects of CSVD on attention and executive functioning are best understood within a network model of cognition as revealed by functional neuroimaging. Analysis of network function in CSVD can improve characterization of disease severity and treatment effects, and it can inform theoretical models of brain function.



*Keywords:* Cerebral small vessel disease; White matter changes; fMRI; EEG; Functional connectivity; Cognition; Cholinergic damage; Aging; Neuroimaging; Vascular cognitive impairment; Alzheimer's disease

## 1. Introduction

Cerebral small vessel disease (CSVD) affects the vasculature of white matter tracts and subcortical structures [1]. On magnetic resonance imaging (MRI) scanning, it is identified by diffuse white matter hyperintensities (WMHs) in periventricular and deep white matter regions and by subcortical/lacunar infarcts [2,3]. CSVD is highly prevalent, with 6–10 times the prevalence of large-vessel stroke [4,5]. Its prevalence is highly correlated with age in those >60 years [6], especially in the presence of vascular risk factors such as hypertension [7,8]. It is the most common cause of vascular cognitive impairment (VCI), a condition encompassing a range of dysfunction from mild cognitive impairment of vascular origin (VaMCI) to vascular dementia (VaD) [1]. CSVD also interacts with and increases the risk of Alzheimer's disease (AD) and other forms of dementia [9–11]. The pathology of CSVD affects distributed systems involved in attention and executive control, manifesting as distractibility and absent-mindedness in

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day-to-day life [12–15]. There is a need, from both clinical and research perspectives, to characterize the neural correlates of this impairment. Although structural neuroimaging measures of CSVD-related changes correspond with this impairment [16–19], they only partially account for the heterogeneity of behavioral outcomes [20,21], with many patients showing no cognitive impairment despite significant lesion burden [22].

In recent years, functional neuroimaging technologies for assessing brain network dynamics have become more accessible [23], with application to clinical conditions affecting distributed network function [24–28], including CSVD, revealing changes inaccessible to standard structural imaging techniques [29,30]. In this article, we systematically review the functional neuroimaging literature on CSVD, focusing on the impact of CSVD on the integrity of distributed brain networks (i.e., pathoconnectomics [31]) supporting attention and executive function. We review both task and resting functional MRI (fMRI) studies and electroencephalography (EEG) studies of CSVD-related changes in frequency spectra and event-related potentials (ERPs). The goal of this review is to provide an overview of the state of knowledge concerning functional neuroimaging changes associated with CSVD to better understand the neural mechanisms of attentional and executive changes associated with this condition and its relationship to neurodegenerative disease, particularly AD.

## 2. Methods

### 2.1. Literature search

A systematic search of the literature was conducted using Medline, PubMed, PsychInfo, and EMBASE databases for articles that met the inclusion criteria. Google scholar was also used to search for gray literature containing additional references to primary literature. Our search strategy mirrored that described in a recent meta-analysis of cerebral small vessel by Wardlaw et al. [32] (see Supplementary Material) with an additional keyword "vascular cognitive impairment." This initial search was concatenated with another search query that was conducted to narrow the articles retrieved to only those involving functional neuroimaging and those investigating cognition rather than motor or sensory function. For the secondary search, the following keywords were used in combination: ("functional neuroimaging" OR "functional magnetic resonance imaging" OR "fMRI" OR "electroencephalography" OR "EEG" OR "event related potential" OR "ERP" OR "neural oscillations") AND ("cognition" OR "cogn*" OR "cognitive change" OR "attention" OR "executive function") NOT ("motor" OR "sensory" OR "somatosensory" OR "somatomotor"). There was no restriction on date of publication and any article published up to June 20, 2014 was examined. Only articles published in English and involving human participants were considered. The reference lists of all research papers meeting inclusion criteria were also searched for potentially relevant articles.

### 2.2. Inclusion and exclusion criteria

We included peer-reviewed articles on brain function and/or connectivity in relation to cognition (i.e., not motor or sensory function) in individuals with CSVD using fMRI or EEG. As papers within the field vary greatly with respect to the terminology used to describe CSVD, we included studies of those classified as having cognitive impairment because of CSVD as defined by impairment in at least one cognitive domain and brain imaging verification of subcortical ischemic vascular disease [33]. Although studies varied with respect to the imaging criteria they used to define CSVD, most papers distinguished CSVD from controls and other diseases based on the presence of extensive periventricular and/or deep white matter lesions and/or the presence of lacunar infarcts. Articles involving patients with VaMCI or VaD were included given that the predominant vascular pathology was not cortical stroke. However, articles involving participants with hereditary causes of CSVD such as cerebral autosomal dominant arteriopathy with subcortical ischemic strokes and leukoencephelopathy were excluded as the focus of this article is on the sporadic type of CSVD.

### 2.3. Screening protocol

All the articles that were identified through the database search (after duplicates were removed) were screened independently for suitability by two authors (A.K.D and V.S.) as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews. Articles were excluded if no abstract was electronically available (e.g., for conference proceedings and commentaries), if the article was a review paper, or if both authors agreed on the basis of the abstract that the article did not meet inclusion criteria. Notably, whereas gray literature, unpublished research findings, book chapters, and review papers were excluded, the reference sections of such items were searched for relevant primary literature. Full texts were obtained for the remaining articles and again assessed by both authors against the inclusion and exclusion criteria. Any disagreements were resolved through in-person discussion, and reasons for exclusion were documented. The remaining articles were included in the review, and their main findings were extracted by A.K.D and summarized in Table 1.

## 3. Results

We identified 470 articles, of which 428 were obtained from the computerized database search and 42 were identified through other sources (e.g., reference lists of relevant

Table 1
Summary of major trends within CSVD functional neuroimaging literature

| Results summary | References | Fig. 3 roman numerals |
|---|---|---|
| 1. Reduced resting and task-related functional connectivity critical to attention related networks such as the FPCN and DMN | [46–52] | V and VI |
| 2. Impaired and compensatory activation within the DAN/FPCN | [38–41] | VII |
| 3. Impaired DMN deactivation/hyper-activation | [42–45] | VIII |
| 4. Reduced power of alpha oscillations and/or increased slow wave activity (EEG slowing) | [66,67,81–91,93] | I and II |
| 5. Functional decoupling (i.e., loss of coherence) of high-frequency oscillations | [69,71,92,94–97] | III |
| 6. Increased latency of ERPs such as the P300/N200 that index information processing | [72–80] | IV |

Abbreviations: CSVD, cerebral small vessel disease; DMN, default mode network; DAN, dorsal attention network; EEG, electroencephalography; ERP, event-related potential; FPCN, frontoparietal control network.

review articles, book chapters, and gray literature). Four hundred one articles were excluded after an initial screening of the abstract or full text (observed $\kappa = 0.816$ [very good], 95% confidence interval: 0.741–0.890). Of the remaining 69 articles that received full review, 47 were eligible for inclusion in the systematic review. These articles were subdivided by the imaging modality used: EEG (n = 31) and fMRI (n = 16). A flowchart of the article selection process is shown in Fig. 1, and most common findings were summarized in Table 1. Descriptions of the various functional imaging techniques and outcome measures used in these studies are summarized in Table 2.

### 3.1. fMRI biomarkers

fMRI measures neuronal activity indirectly through the blood oxygen level–dependent (BOLD) signal. During task-based fMRI studies, participants are exposed to different stimulus/behavioral conditions designed to induce measurable BOLD signal changes. Such studies are important to probe the functional neuroanatomy of specific tasks, as indicated by task-related activation maps and connectivity patterns. In resting-state fMRI (rs-fMRI), brain activity is estimated on the basis of synchrony of spontaneous low-frequency fluctuations (<0.1 Hz) in the baseline BOLD

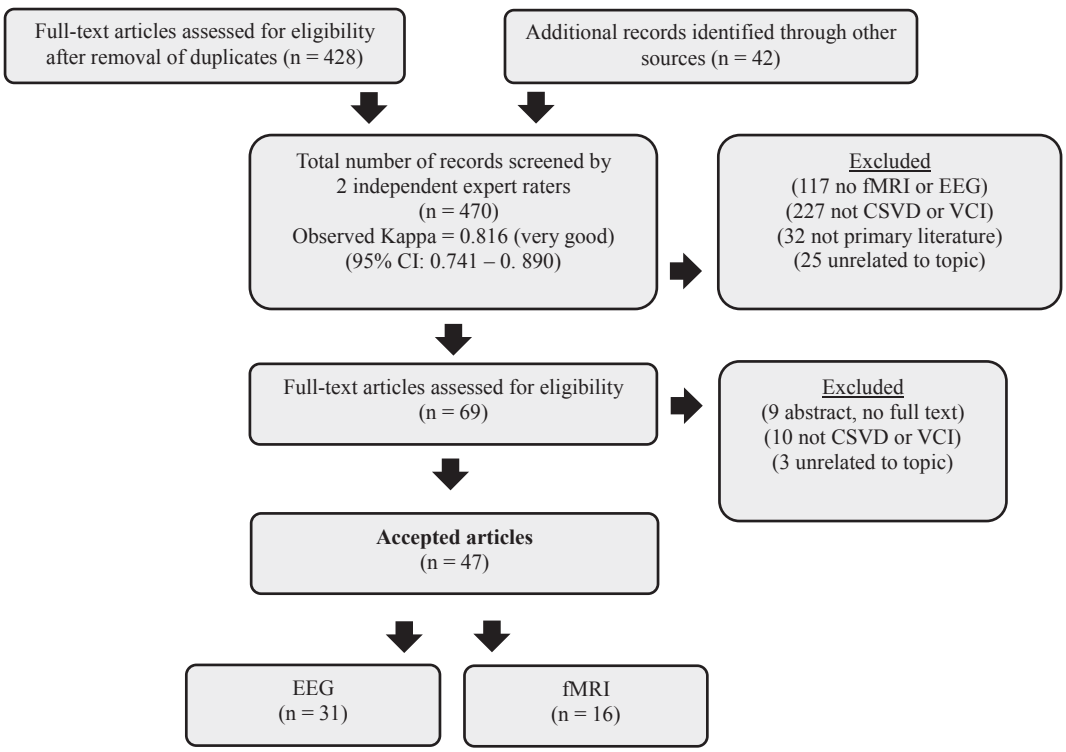


Fig. 1. Article screening flowchart. Computerized databases were searched on June 20, 2014 using the search strategy described in the Supplementary data. Two authors (A.K.D. and V.S.) independently screened all the papers that were retrieved from the search (n = 470). Full texts were obtained for 69 of the articles that were again independently assessed for eligibility by A.K.D and S.V. Articles were excluded on the basis of inclusion and exclusion criteria. Ultimately, a total of 47 articles were included in the systematic review with trends summarized in Table 1. These articles were subdivided into groups on the basis of the imaging tool used (i.e., electroencephalography [EEG] or functional magnetic resonance imaging [fMRI]). Abbreviations: CSVD, cerebral small vessel disease; VCI, vascular cognitive impairment; CI, confidence interval.

Table 2
Descriptions of major techniques/methods

| Techniques | Description |
|---|---|
| Task fMRI | A subtype of BOLD fMRI wherein the signal is observed during performance of a task. In task-based experiments, participants are exposed to different stimulus/behavioral conditions designed to induce measurable BOLD signal changes. |
| Rs-fMRI (intrinsic connectivity analysis) | Another subtype of BOLD fMRI that does not require participants to perform any behavioral tasks. Rather, brain activity is estimated on the basis of the intensity and synchrony of spontaneous low-frequency fluctuations (<0.1 Hz) in the baseline BOLD signal within and between brain regions. Connectivity in this context refers to synchrony between spatially distinct brain regions in the pattern of spontaneous fluctuations of the BOLD signal. Structures that demonstrate synchrony beyond what would be predicted by chance are said to be "functionally connected" and are part of a common network. Task-free analysis of ICNs may help elucidate the neural architectures that support fundamental aspects of human behavior. |
| ERPs | ERPs reflect the summed activity of postsynaptic potentials generated by a population of brain structures that fire in synchrony in response to a specific event or stimulus. They are commonly used as indices of mental processing that are highly reproducible. ERPs enable study of the time domain of EEG. |
| EEG power spectrum analysis | Fourier analysis can be used to decompose continuous EEG data into a voltage by frequency graph referred to as a power spectrum, with power being the square of the EEG magnitude. Power spectrum analysis typically involves the decomposition of raw EEG into a set of five standardized spectral (frequency) bands to better study patterns of spontaneous neural oscillatory activity. Power spectrum analysis enable study of the frequency domain of EEG. |
| EEG coherence analysis | EEG coherence is generally interpreted as a measure of functional association or coupling between anatomically distinct brain regions. EEG coherence measures are based on the covariance in the power spectrum between two or more electrode locations. It serves as a coarse measure of temporal synchronicity of coupled rhythmic EEG oscillations of two neural populations. |

Abbreviations: BOLD, blood oxygen level–dependent; rs-fMRI, resting-state functional magnetic resonance imaging; ERP, event-related potential; EEG, electroencephalography; ICN, intrinsic connectivity network.

signal between brain regions [34], identifying intrinsic connectivity networks (ICNs). In this review, we focus on the dorsal attention network (DAN), the frontoparietal control network (FPCN), and the default mode network (DMN). These networks are well-established in the cognitive neuroscience literature [35,36] and correspond to the attention and executive functioning deficits most commonly affected by CSVD [37]. In the context of VCI, activation and rs-fMRI studies have revealed changes in regional neuronal activity and functional connectivity associated with CSVD. Specifically in reviewing the literature, the three most common changes associated with VCI-CSVD include 1) BOLD signal activation changes across nodes of the FPCN that is related to degree of cognitive impairment [38–41]; 2) impaired DMN deactivation or hyperactivation [42–45]; and 3) reduced functional connectivity within and/or between nodes of the FPCN, DAN, and DMN [46–52].

### 3.1.1. Activation changes across nodes of the DAN/FPCN

Activation fMRI paradigms have documented BOLD signal changes in relation to cognitive performance in individuals with mild-severe CSVD. In a study comparing patients with mild nondemented VCI, subcortical VaD, and older adults during performance of a color–word Stroop task [39], those with VaD exhibited decreased activity within key structures across the DAN/FPCN (i.e., bilateral dorsal anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), inferior frontal gyrus, anterior inferior parietal lobule, and insula) relative to controls, whereas those with mild VCI exhibited greater activation in these regions. Across the patient groups, lower prefrontal activation was associated with slower reaction time. These differences in activation patterns were interpreted as reflecting dysfunction in subcortical VaD (severe CSVD) and compensation in those with mild VCI (mild CSVD). Two other studies have reported inverse relationships between CSVD severity (as measured by WMH burden) and bilateral PFC and ACC activation—with lower activation also being associated with worsening behavioral performance on tests of working memory and executive function [40,41]. We should note that one of these studies [40] also reported evidence of compensatory activation, with better performance in those with high WMH burden associated with greater activity in the posterior parietal cortex. Age-related changes in prefrontal activity have been widely reported, with older adults demonstrating greater activation relative to younger adults even when performance is age equivalent [53]. However, as many of these aging studies do not take into consideration white matter lesion load, it is possible that CSVD could be contributing to these findings. Indeed, the association between behavior and compensatory neural activation after white matter damage has been reported in other patient populations with white matter injury such as diffuse axonal injury [27] and multiple sclerosis [54].

### 3.1.2. Altered function within the brain's intrinsic networks

Although regional changes in brain activation are associated with CSVD, successful execution of cognitive tasks depends not only on the integrity of isolated brain regions but also on the integrity of brain network function. As such, regional changes in activation and deactivation patterns, as revealed by traditional functional neuroimaging analysis techniques, provide limited information on the nature of the network dysfunction of CSVD. More recent techniques

emphasize ICN analysis at rest or during task performance. The DAN, in collaboration with the FPCN, plays an important role in goal-directed attention [55]. The DMN is anticorrelated with the DAN and most active when the mind is at rest and/or engaged in self-referential "stimulus-independent" thought [56]. Connectivity between the DMN and FPCN correlates with working memory performance, with momentary lapses in attention being associated with reduced task-related deactivation of the DMN [57,58] and reduced prestimulus activity within the frontal control regions [59] (Fig. 2). Subsequently, we review how activity within and between these networks is affected by CSVD.

Impaired functional connectivity between nodes of the DMN suggests that CSVD contribute to DMN dysregulation and cognitive impairment through damage to white matter tracts traveling within and between frontal and parietal regions [46]. Indeed, reduced connectivity between nodes within the DMN is related to white matter lesion load [50,52]. Patients with asymptomatic carotid stenosis, a condition that would result in damage similar to that seen in CSVD, show decreased intrahemispheric functional connectivity between the posterior cingulate cortex (PCC), hippocampus, and medial prefrontal cortex (mPFC) relative to controls [46]. Increased mPFC-parietal connectivity is related to memory test performance in individuals with CSVD, but only among those with gray matter atrophy, suggesting compensation [51]. Decreased connectivity across DMN nodes in CSVD was related to increased amplitude of spontaneous low-frequency oscillations in the posterior DMN (PCC and hippocampus) and decreased amplitude in the anterior DMN (mPFC) [49]. Cognitive impairment in CSVD was associated with reduced PCC connectivity to anterior structures (e.g., bilateral middle frontal gyrus and left ACC) and enhanced connectivity to more posterior structures (e.g., left middle temporal gyrus [MTG] and the left superior parietal lobule [SPL]) [47]. Taken together, these findings suggest that CSVD affects long-distance anterior-posterior connectivity within the DMN that contributes to network dysfunction and cognitive impairment [51].

Suppression of the DMN is considered important to the online maintenance of task-related goals [59–61] (but see Spreng et al. [62]). CSVD is associated with reduced DMN deactivation during task performance [42,43]. Using a visual n-back working memory task, those with VaMCI demonstrated reduced task-induced deactivation in DMN regions with increasing working memory load relative to those with non-vascular MCI and older adults [42]. Similarly, hyperactivation of the rostral ACC, a key DMN structure,

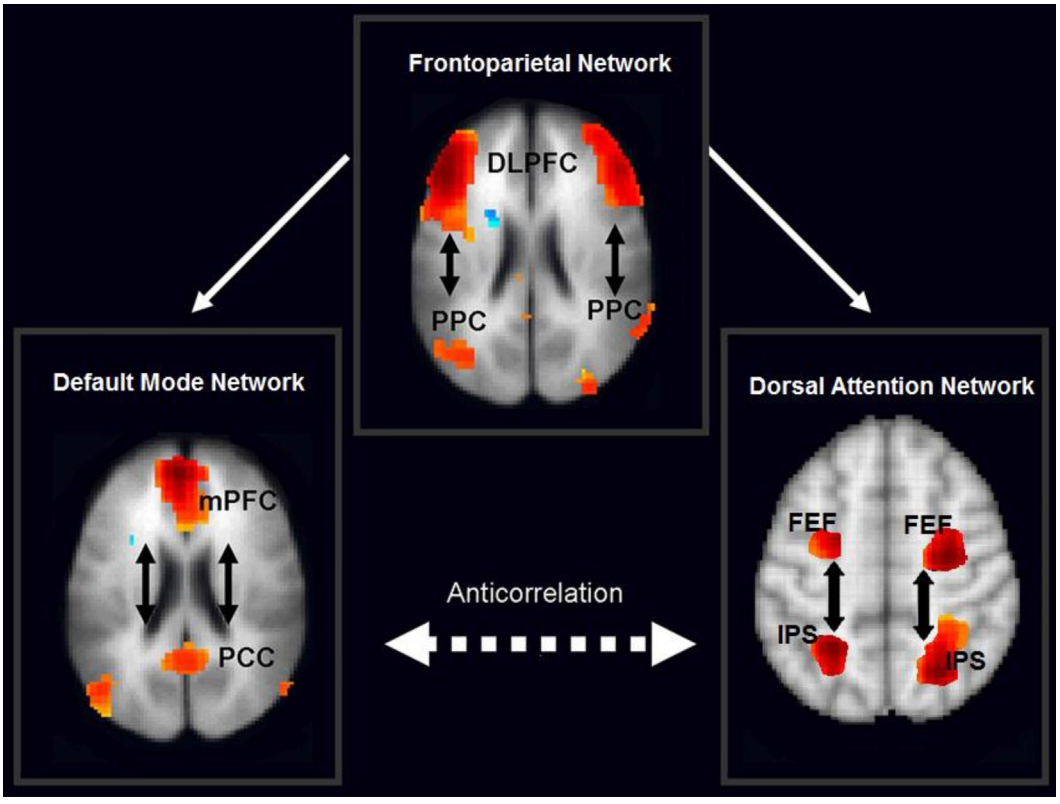


Fig. 2. Major attention networks and their hubs. Three common attention networks are the default mode network (DMN), the frontoparietal control network (FPCN), and the dorsal attention network (DAN). These three networks are interrelated. Although activity within the DMN and DAN is typically anticorrelated, the FPCN is believed to support both networks depending on task demands. Major hubs of these networks include the medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC) for the DMN, the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC) for the FPCN, and the frontal eye fields (FEF) and the area around the intraparietal sulcus (IPS) for the DAN. Adapted from Nekovarova et al. [141].

during an affective-reactivity task was correlated with WMH burden [43], an effect accentuated by depression. Rostral ACC hyperactivation was similarly noted in another study in association with high WMH burden, accompanied by reduced DLPFC activation during working memory task performance [44]. The DLPFC is a critical part of the DAN/FPCN and is thought to play a major role in goal maintenance. DLPFC dysfunction may represent a failure of frontal structures to regulate DMN activity, thus contributing to impaired DMN deactivation.

Functional connectivity abnormalities implicating the FPCN have also been reported [44,46,48,52]. As previously mentioned, goal maintenance, which refers to the ability to actively maintain goals to accomplish a task, is involved in many cognitive tasks and involves the DLPFC within an associated network of regions [63]. In normal aging, attention-related enhancement of functional connectivity between the DLPFC and other FPCN regions can be observed relative to younger adults. This enhancement of connectivity is lacking in older adults with CSVD [44], suggesting that network disruption in CSVD impairs the ability to upregulate activity in the DLPFC when goal maintenance is required.

In summary, growing evidence suggests that CSVD is associated with reductions in functional connectivity within the DMN and FPCN/DAN that reflects strategic ischemic damage to corticocortical and corticosubcortical circuitry. This network dysfunction provides clues as to the mechanisms of cognitive decline in CSVD. For example, CSVD may interrupt network interactions allowing goal-irrelevant information to interfere with the contents of working memory.

### 3.2. EEG biomarkers

EEG recordings provide a measure of electrical brain activity over time using scalp electrodes, reflecting the amalgamation of many underlying ongoing brain processes [64]. EEG can be studied within the time domain (i.e., analysis of ERPs) and within the frequency domain (i.e., power spectrum analysis). When averaging is time locked to stimulus onset (e.g., the presentation of a sound or image), brain ERPs can be measured that vary with respect to polarity, amplitude, latency, and scalp distribution. The high temporal resolution of ERPs permits inferences regarding the time course of cognitive processes not possible using fMRI [65]. Fourier transformation can be used to decompose continuous EEG data into a voltage by frequency graph referred to as a power spectrum, with power being the square of the EEG magnitude. Power spectrum analysis typically involves the decomposition of raw EEG into a set of five standardized spectral (frequency) bands to better study patterns of spontaneous neural oscillatory activity. These bands are thought to arise from relatively independent functional systems and are conventionally defined as delta ($\Delta$ = 1.5–4 Hz), theta ($\theta$ = 4–8 Hz), alpha ($\alpha 1$ = 8–10.5 Hz and $\alpha 2$ = 10.5–13 Hz), beta (13–25 Hz), low gamma (25–70 Hz), and high gamma (>70 Hz) [66]. Relative power of EEG oscillatory activity is believed to reflect interactions between local groups of excitatory and inhibitory neurons, with high-frequency bands mainly mediated by reciprocal corticocortical connections and lower frequency oscillations (i.e., delta waves) being mediated by regulatory interactions between cortical and subcortical structures that are normally inhibited during wakefulness [67]. Although higher frequency bands are generally associated with higher order cognitive processes such as attention and working memory, alpha band activity is associated with inhibition of both external and internal cognitive processes [68].

Power spectrum data can also be used to study the functional association or coupling between anatomically distinct brain regions through analysis of EEG coherence [69]. Similar to fMRI connectivity measures, EEG coherence measures are based on the covariance in the power spectrum between two or more electrode locations. It is a measure of temporal synchronicity of coupled rhythmic EEG oscillations of two neural populations that may be anatomically linked via corticosubcortical/corticocortical connections [70,71].

CSVD is associated with increased latency of ERPs such as the P300 and N200 that index information processing [72–80], reduced power of alpha oscillations and/or increased slow wave activity [66,67,81–91], and reduced EEG coherence of alpha oscillations [69,71,92–97].

#### 3.2.1. Increased latency of the P300 and N200 ERP

The P300 is a robust ERP component that is a marker of attentional and working memory processes wherein latency and amplitude reflect stimulus classification speed and extent of attentional allocation, respectively [98,99]. Possible generator sites for the P300 include the thalamus, insula, and the right medial frontal gyrus [100,101]. It is most commonly studied using an auditory oddball task in which individuals are presented with a continuous stream of stimuli and are asked to detect the presence of distinct target stimulus that occurs infrequently relative to all other stimuli (e.g., tone of a higher pitch). The task requires participants to maintain attention and discriminate between target and nontarget stimuli. To date, the P300 has been used to study a number of psychiatric and neurological disease states and aging [102,103]. The P300 comprised two distinguishable subcomponents: the P3a and P3b [104]. For the purposes of this review, references to the P300 will primarily refer to the P3b that is related to the effortful processing of task-related events.

The N200 (particularly the N2b subcomponent) is also thought to reflect executive functions and is commonly elicited by go/no-go tasks in response to no-go trials [105]. The N200 component responds functionally much like the P3b component, and as such, they are often researched together. Increase in N200 amplitude is hypothesized to represent the effort required to sustain inhibitory control, whereas latency is correlated with response time.

A third of the 31 EEG studies reviewed investigated the P300 and/or N200 using an auditory oddball task [72–80]. Of these studies, with the exception of an early investigation involving normal aged subjects [77], all reported increased latency of the P300 [74,75,78,79,106], N200 [76], or both [73,80] in CSVD, suggesting slowing of cognitive processing. Increased latency was also commonly associated with impaired performance on neuropsychological tests such as Part B of the Trail Making Test [74,75] and was more pronounced when leukoaraiosis extended past the periventricular region into the centrum semiovale [72].

With respect to its diagnostic potential, P300 abnormalities appear at a much earlier stage in CSVD relative to AD [80], possibly because early degenerative processes in AD may spare the neural substrates of attention. The P300 has also been reported to be sensitive to pharmacological intervention. For example, intravenous treatment with amantadine sulfate, a dopamine agonist that helps modulate glutaminergic transmission within the central nervous system, was found to shorten P300 latency in association with improved neuropsychological test performance [74]. This suggests that CSVD affects speed of processing through impaired conduction of electrical signals and through promotion of neurotransmitter imbalance that may be partially amenable to pharmacological intervention. Although abnormalities in the P300 are not specific to CSVD, the P300 can be used as an adjunct tool for objectively screening for declines in speed of processing that accompany CSVD.

#### *3.2.2. Reduced alpha power and increased slow wave activity*

Time-frequency analysis of EEG has also shown promise in its utility as a biomarker of CSVD effects. As early as mid-1990s, increases in slow delta (Δ) wave activity have been reported in those with clinical evidence of subcortical ischemic damage [85–87,91]. More recent investigations have echoed these claims and have additionally reported reductions in α2 wave activity in relation to increasing white matter pathology [82,83]. Increased (delta + theta)/(alpha + beta) ratio not only correlates with volume of WMHs but is also sensitive to the presence of recent ischemic lesions [83].

The loss of faster oscillations and increase in slow activity is thought to be related to weakening of the negative feedback loop of inhibitory and excitatory neurons that govern thalamocortical interactions and may contribute to changes in functional activity detected by fMRI [67,107]. Reduced α1 power density among those with CSVD (relative to controls and those with nonvascular MCI) has been traced to the precuneus, cuneus, middle occipital gyrus, and PCC—regions that are also part of DMN [84]. These reductions were also found to be associated with poor performance on tests of working memory, verbal fluency, and reasoning.

Similar reductions in alpha power within posterior regions have also been reported among those with subcortical VaD [67,89,90], with evidence that the degree of such cerebrovascular-related changes falls between normal aging and nonvascular MCI [66,81]. This suggests that thalamic neural oscillations may be more sensitive to neurodegenerative processes than to global ischemic white matter burden. These studies, however, used global measures of white matter damage (qualitative visual scales) making it difficult to disentangle the impact of lesion location. This is important as power spectrum changes could be related to damage to the cholinergic system that provides regulatory input to the thalamus. Indeed, there is converging evidence that these changes are partially driven by ischemic damage to cholinergic fibers, suggesting a mechanism for the link between CSVD and AD [69,71,93].

#### *3.2.3. Reduced EEG coherence/functional decoupling of high-frequency oscillations*

CSVD is also associated with reduced EEG coherence of high-frequency oscillations. For example, periventricular WMHs are reportedly associated with reduced coherence (across high-frequency bands) between nodes of the PFC and between nodes of the visual association network [94]. Decreased intrahemispheric frontoparietal EEG coherence across high-frequency bands (α, β, and γ), in association with poorer scores on tests of executive function and increasing structural damage, has also been reported in those with CSVD relative to those with nonvascular MCI and healthy controls [71,96]. In contrast, increased interhemispheric coherence in the delta frequency band across frontal regions [96] was reported in those with nonvascular cognitive impairment relative to those with CSVD, demonstrating a functional dissociation between vascular and nonvascular causes of cognitive impairment. Ischemic damage to cholinergic tracts was found to strongly mediate the relationship between CSVD and global loss of functional coherence of alpha rhythms [69], particularly when damage occurred within the long-range capsular pathway [95]. Finally, CSVD is associated with reduced directionality of information flow, which normally travels parietal to frontal, affecting functional coupling of EEG rhythms in the θ, α1, α2, and β1 (13–20 Hz) frequency bands [92].

## 4. Discussion

Converging evidence suggests that cognitive impairments due to CSVD result from disruption of frontosubcortical circuits and long-distance association fibers that in turn impair communication between critical neural networks responsible for cognitive control of attention such as the DMN, FPCN, and DAN. With respect to hemodynamic markers, CSVD appears to be associated with impaired deactivation/hyperactivation of the DMN, functional differentiation and compensatory activation changes across the FPCN/DAN, and decreased functional connectivity between

anterior and posterior brain regions affecting both the FPCN and DMN. These findings are complemented by electrophysiological studies reporting decreased EEG coherence of high-frequency oscillations between anterior and posterior regions, delayed latency of ERPs in support of reduced network efficiency, and an overall shift toward slower wave activity (e.g., reduced alpha power and increased delta wave activity) that may be driven by ischemic damage to cholinergic tracts and other neuromodulatory axonal projections [108]. Together, these studies provide compelling evidence that behavioral phenotype observed in those with VCI because of CSVD is the result of uncompensated disruption of critical functional brain networks. Furthermore, ischemic damage to cholinergic tracts also highlights a potential link between CSVD and AD with comorbid cerebrovascular disease lowering the threshold for expression of dementia.

### 4.1. Neurophysiological underpinnings of CSVD effects

CSVD results in reduced blood flow through deep penetrating arteries of the brain that supply thalamic nuclei and their cortical projections. Of particular interest include branches of the posterior cerebral artery that supply regions of the thalamus and lenticulostriate arteries that in turn supply regions of the internal capsule [109]. Partial occlusion of these end arteries results in damage to white matter tracts that are sensitive to ischemia. Venous collagenosis is also thought to contribute to CSVD pathology through vasogenic edema and compromised circulation of interstitial fluid [2]. Whereas direct damage to either the anterior or the dorsomedial thalamic nuclei would result in classic lacunar stroke dysexecutive symptoms, damage to projection fibers, particularly as they pass through the internal capsule, or association fibers that often pass through periventricular regions, would likely have downstream effects with respect to impairing communication within and between anterior and posterior brain regions implicating critical networks such as the DMN, FPCN, and DAN. Additionally, strategic damage to cholinergic tracts traveling from the nucleus basalis of Meynert to their synaptic endings in the neocortex may weaken the negative feedback loop of inhibitory and excitatory neurons that govern thalamocortical interactions, resulting in the loss of faster oscillations and increase in slow wave activity that is typically associated with low arousal (see Fig. 3). Overall, this lesion profile fits with the behavioral profile of cognitive impairment in those with CSVD that is characterized by cognitive slowing during executive function tasks and difficulty staying on task and maintaining goals in mind when solving problems [110,111].

### 4.2. Integrated network disruption/disconnection hypothesis and model

In Fig. 3, we outline a hypothetical model illustrating the relationship between CSVD, diffuse network disruption, and damage to cholinergic fibers. In this model, critical hubs within the FPCN (green) and DMN (blue) are highlighted. Consolidating reported imaging findings, damage to connections of the PFC results in network-wide effects such as reduced DMN and FPCN connectivity [46], reduced anterior-posterior (frontoparietal) EEG coherence [71,92], changes in regional activation patterns [49], and overall slowing of information processing as indexed by the P300 ERP [72–80].

Specifically, damage to anterior-posterior fibers that connect the DLPFC to the intraparietal sulcus could explain reports of DLPFC hypoactivation and compensatory ACC hyperactivation [44]. Similarly, damage to anterior-posterior fibers that connect the medial PFC to the PCC may explain reports of impaired DMN deactivation with increasing working memory load because of reduced prefrontal modulation by the PCC [112]. This interplay between regional changes in connectivity and activation is consistent with the recently proposed "less wiring, more firing" hypothesis [113].

This pattern of reduced anterior–posterior communication is echoed in the EEG literature with reports of VaMCI being associated with increased frontoparietal EEG coherence in the delta frequency band (i.e., increase pathological slow wave activity) and decrease of EEG coherence in high frequencies (i.e., alpha, beta, and gamma frequencies: 7–45 Hz) proportional to the extent of anatomical subcortical vascular damage (including cholinergic damage) [96]. In the healthy, waking brain, suppression of lower frequency and increase in higher frequency spectra reflect corticothalamic communication mediated through cholinergic activity, supporting arousal and conscious attention. Similar frequency band abnormalities have been reported in a wide array of neurological and psychiatric illnesses [114,115]. Moreover, damage to white matter tracts also has a negative influence on processing speed that strongly correlates with P300 ERP latency [79].

Relating EEG and fMRI measures, the DMN is held to modulate low-frequency alpha rhythms during wakeful rest. This is supported by the evidence that transcranial magnetic stimulation (TMS) inhibition of the angular gyrus (a DMN hub) results in both enhanced alpha power within the occipital–parietal cortex and intrahemispheric alpha coherence (8–10 Hz) [68]. This negative correlation between posterior alpha power and DMN activity has also been reported in healthy adult populations [116]. Overall, this is consistent with reports of decreased posterior alpha power [81,82,93] and impaired DMN deactivation [112]/posterior midline hyperactivation [49] in those with CSVD. Relating back to our model, damage to frontosubcortical circuits results in unchecked DMN activity that in turn may be responsible for reduced posterior alpha activity.

### 4.3. Relationship between CSVD and AD

The model presented in Fig. 3 also highlights the relationship between CSVD and the cholinergic system

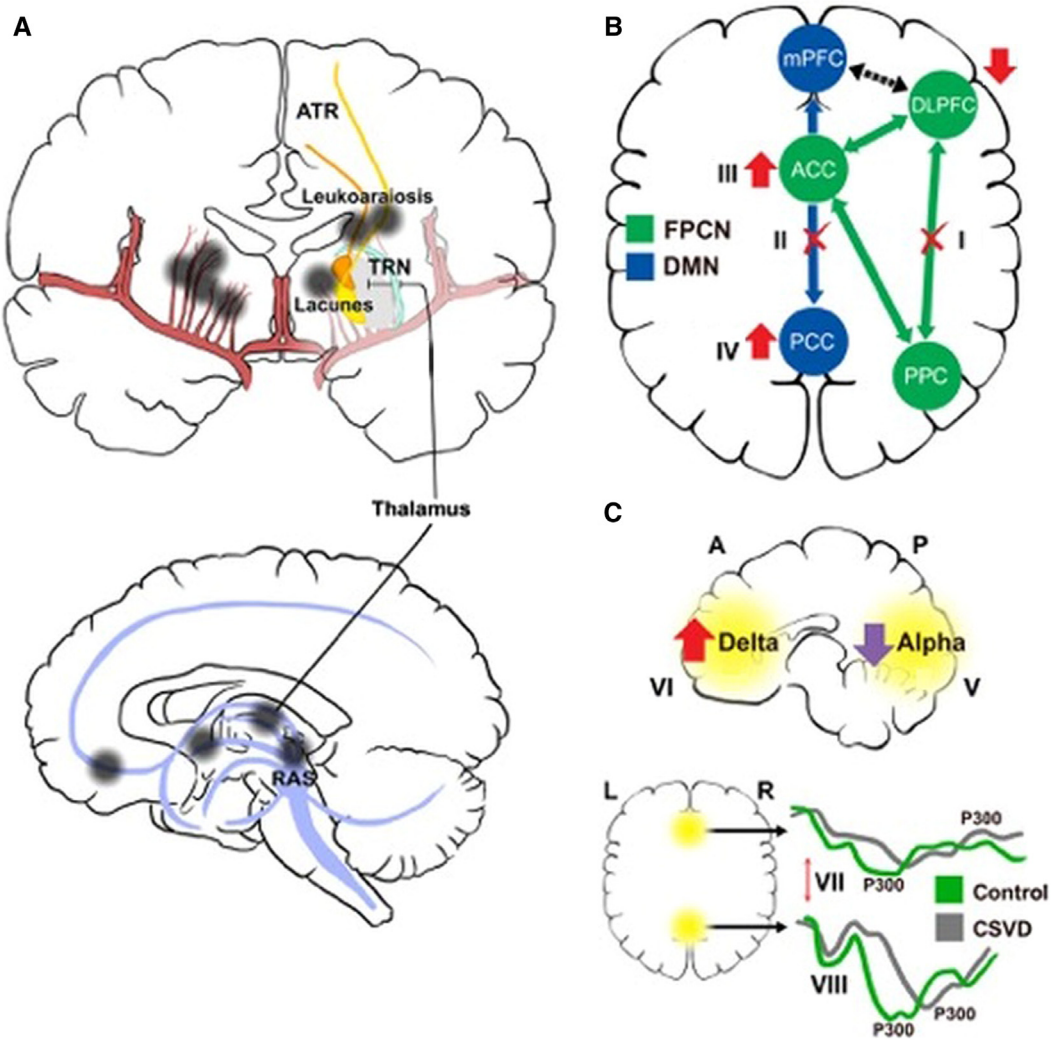


Fig. 3. Distributed network disruption and interference hypothesis. (A) Cerebral small vessel disease (CSVD) is a heterogeneous disorder of the brain's microvasculature that affects the circulation of blood through the small perforating end arteries of the brain. CSVD is associated with ischemic damage to subcortical brain regions (e.g., lacunes within anterior/dorsomedial thalamic nuclei), white matter fibers such as thalamocortical projection fibers (e.g., anterior thalamic radiations [ATRs] and long association fibers), and cholinergic circuits of the basal forebrain and rectricular activating system (RAS) that regulate arousal. Dark regions represent areas of ischemia. Damage to cholinergic inputs to the thalamic rectricular nucleus (TRN) in particular may weaken the negative feedback loop of inhibitory and excitatory neurons that govern thalamocortical interactions. (B) Reduced cholinergic input to the thalamus may explain reports of reduced alpha wave activity (I) [82], increased delta wave activity (II) [82], and reduced frontoparietal EEG coherence (III) [66]. Damage to association and projections fibers also negatively influence processing speed as indexed by the P300 event-related potential, which is prolonged in those with CSVD (i.e., increased latency) (IV) [73]. (C) Damage to long association fibers may also manifest as reductions in functional connectivity between major nodes of the default mode network (DMN, blue, V) [49] and frontoparietal control network (FPCN, green, VI) [46]. Specifically, damage to anterior-posterior fibers that connect the dorsolateral prefrontal cortex (DLPFC) to the posterior parietal cortex (PPC) may explain reports of DLPFC hypoactivation and compensatory anterior cingulate cortex (ACC) hyperactivation (VII) [40,44]. Similarly, damage to anterior-posterior fibers that connect the medial prefrontal cortex (mFPC) to the posterior cingulate cortex (PCC) may explain reports of failed DMN deactivation with increasing working memory load (VIII) [44]. Red X's refer to weakened functional network connections. The black dotted pathway refers to communication between the DMN and FPCN through the medial prefrontal cortex (mPFC). Note: the ACC is not part of the DMN. Roman numerals are cross-referenced to the neuroimaging findings listed in Table 1.

(highlighted in purple in panel a). According to the cholinergic hypothesis, deterioration of cognitive function in those with AD can be attributed in part to degeneration of basal forebrain cholinergic neurons and reduced cholinergic neurotransmission [117]. Damage to long- and short-range cholinergic tracts can be indexed by changes in spectral power density of brain regions [95]. Accordingly, AD has been consistently linked to increased delta and theta and reduced alpha (8–13 Hz) and beta frequency activity (13–30 Hz) relative to those with MCI and healthy aged-matched controls—in agreement with changes in regional cerebral blood flow, metabolism, and global cognitive function [70,118]. Interestingly, this pattern of EEG modification has also been reported in those with VaMCI because of CSVD [69,71,84,92,96], suggesting a possible link between CSVD and AD, with CSVD increasing one's susceptibility toward developing dementia and independently exacerbating cognitive dysfunction [119].

Indeed, in those with VaD, ischemic damage within cholinergic pathways has been shown to be more predictive of dementia severity than total white matter lesion volume [120], with cholinesterase inhibitors such as donepezil [121] and galantamine [122] demonstrating promise in improving cognitive function. Indeed, AD patients with subcortical hyperintensities along cholinergic pathways are more responsive to cholinergic therapy, particularly on frontal/executive tasks [123].

### 4.4. CSVD and heterogeneity

CSVD is a heterogeneous condition that may result in ischemic damage to connections between any of the nodes within the DMN, DAN, and particularly the FPCN that is thought to coordinate with both the DMN and DAN [124]. Although there have been attempts to provide objective cut-off values to distinguish symptomatic white matter changes (characteristic of CSVD) from asymptomatic changes [125], the clinical manifestation of CSVD-related deficits depends not only on the volume of ischemic damage but on the placement of such lesions. Although the probability of affecting critical networks increases with greater WMH volume, damage to anterior or dorsomedial thalamic nuclei or their projection fibers along the anterior limb of the internal capsule would be particularly detrimental given the high concentration of tracts traveling through that region [108]. Thus, relation of CSVD to local activity in specific network nodes will be a less fruitful approach than one which considers cognition as an emergent property of network activity [126,127]. Functional connectivity analyses emphasize the degree of covariation in the functional activity of a network of brain regions, providing a measure of how well information processing is shared between different regions and, therefore, permitting evaluation of efficiency of cognitive processes [128] (Table 2). Rather than attempting to pinpoint the exact location of the lesion, a more practical biomarker is assessing changes in regional and global network efficiency [55,129]. Graph theoretical modeling has become an increasingly popular approach to characterize such changes in disorders such as traumatic brain injury [130], AD [131], epilepsy [132], and schizophrenia [133] (for review, see [134]).

### 4.5. Differentiating vascular and non-vascular cognitive impairment using functional imaging

At the group level, VCI resulting from CSVD can be distinguished from nonvascular MCI in the extent of DMN deactivation [112], the nature of EEG coherence changes [95,96], and in the distribution of EEG coherence changes [71]. DMN deactivation during task performance is intact in nonvascular MCI, yet reduced in those with CSVD [112]. With respect to power spectrum changes, cognitive impairment related to medial temporal lobe damage (as in MCI) differs from VaMCI as nonvascular MCI is associated with modification of EEG coherence in low frequencies without changes in the fast frequencies [95,96]. Finally, whereas in VaMCI, functional changes primarily involve frontoparietal regions, nonvascular MCI is primarily frontotemporal [71]. Overall, this suggests that EEG and fMRI measures of functional activity/connectivity may be useful in distinguishing the primary cause of impairment in those who present with mixed dementia or MCI, helping to differentiate vascular from nonvascular causes [135]. Individuals with both pathologies are expected to show neuroimaging features of both diseases, with clinical concordance in relation to mnemonic and attentional changes.

### 4.6. Limitations and future directions

Although our systematic review reflects an exhaustive summary of the state of the field, we acknowledge the limitation of excluding of gray literature (i.e., studies not published in a traditional journal format), which may introduce a publication bias. Also as this is a systematic, qualitative review of the literature rather than a quantitative review (wherein effect sizes are extracted for specific outcome measures), reporting of an estimate of publication bias was unfeasible. Next, given the heterogeneity of CSVD, the studies reviewed varied greatly with respect to diagnostic criteria used to define groups, capturing a wide spectrum of VCI disorders. Moreover, studies also greatly varied with respect to the methodology used to analyze the data. Many of the reviewed studies also failed to successfully link imaging findings to differences in behavior, despite reporting significant group effects.

To enhance generalization, future investigations should strive to characterize white matter burden volumetrically, utilize more targeted cognitive assessment tools and apply multivariate techniques toward the analysis of brain-behavioral relationships.

Future studies should also incorporate the full spectrum of CSVD and associated brain atrophy when studying the relationship between fMRI and EEG measures with cognitive impairment. Although it is known that cerebral microbleeds, enlarged perivascular spaces and micro-infarcts do contribute to the clinical manifestation of CSVD independent of WMH, their impact on functional brain activity remains largely unknown–representing a considerable gap in the literature. It is also important that future studies consider how associated brain atrophy (regional and/or global) impacts functional activation/connectivity independent of the aforementioned SVD markers. Brain atrophy has been associated with changes in DMN connectivity [136], increased local BOLD activity [137], and EEG power spectrum abnormalities [138]. As such failing to correct for atrophy may distort interpretation of imaging findings.

Additionally, future studies should use more ecological activation paradigms beyond popular tasks such as the

auditory oddball task that was used in most ERP studies. Also, in light of growing concerns of the confounding effects of impaired neurovascular coupling in patients with cerebrovascular disease [139,140], future studies should also focus on pairing fMRI with more direct measures of cognitive processing such as EEG. Simultaneous acquisition of EEG and fMRI to study the effects of CSVD would take advantage of the strengths of each modality and likely yield novel insights through converging hemodynamic and electrophysiological measures, although this kind of multimodal imaging is not widely available. Finally, investigators should also consider including comparison groups with vascular risk factors but no evidence of cognitive impairment, as those without vascular risk factors may not be representative of the general population but rather represent the "super healthy." Such an approach can help researchers pursue questions regarding what differentiates those who develop cognitive impairment from those who do not.

## 5. Conclusions

On the basis of converging hemodynamic and electrophysiological evidence, we hypothesize that cognitive impairment because of CSVD results from diffuse disruption of frontosubcortical circuits including cholinergic white matter tracts and reduced long-distance connectivity within the FPCN, DMN, and DAN. Slowed processing speeds and poor regulation of goal-directed attention may be the product of reduced network connectivity and global network dysfunction. Although the overall volume of white matter changes plays a role in clinical expression, it appears that the type and location of the lesion are of equal importance.

Overall, moving forward, functional neuroimaging of CSVD should help to resolve the clinical heterogeneity of the disease and provide targets for developing and evaluating the effects of novel cognitive and pharmaceutical interventions. Indeed, there are several clinical trials underway that include analysis of resting-state connectivity such as the second iteration of the Alzheimer's disease Neuroimaging Initiative 2.

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## Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jalz.2016.01.007.

## RESEARCH IN CONTEXT

1. Systematic Review: Articles on functional neuroimaging of cerebral small vessel disease (CSVD) were identified through literature search. Functional MRI (fMRI) studies reported reduced functional connectivity or disrupted connections across distributed brain networks in CSVD. EEG studies indicated functional decoupling of high frequency oscillations, increased slow wave activity and increased latency of event-related potentials.
2. Interpretation: A model of integrated network disruption and interference was formulated. This model holds that cognitive impairment in CSVD results from diffuse disruption of fronto-subcortical circuits including cholinergic white matter tracts and reduced long-distance network connectivity. This in turn causes slowed processing speed and impaired goal-directed attention that are characteristic of CSVD and exacerbate functional decline, especially in the presence of co-morbid Alzheimer's disease.
3. Future directions: Functional neuroimaging may be able to aid in the identification of subgroups within CSVD and to distinguish CSVD from other forms of dementia. Application of modern multivariate techniques for analysis of brain network dynamics should improve the assessment CSVD brain effects, ultimately assisting in the development and evaluation of new interventions.

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