REVIEW ARTICLE

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MRI-defined vascular depression: a review of the construct

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Objective: To review the construct of MRI-defined vascular depression and to examine the substantive and methodological issues that bear on its validity as a distinct subtype of depression in late life.

Design: Literature review.

Results: We identified three areas that are critical to establishing the validity of MRI-defined vascular depression: (1) understanding and delineating the relationship between MRI hyperintensities, executive dysfunction, and antidepressant treatment outcome; (2) understanding the relationship between, and establishing the validity of, qualitative and quantitative approaches to the measurement of MRI hyperintensities (the primary feature of the proposed subtype); (3) establishing the clinical presentation and course of the subtype in the context of other late-life disorders.

Conclusions: Despite considerable data supporting the validity of MRI-defined vascular depression, there are a number of critical issues that remain, including establishing a causal relationship between cerebrovascular disease and late-life depression, establishing consistent diagnostic criteria, determining the importance of lesion type and location, and understanding the course of the disorder. Copyright © 2010 John Wiley & Sons, Ltd.

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Introduction

Vascular depression (VD) has been proposed as a unique subtype of late-life depression (LLD) (Hickie *et al.*, 1995; Krishnan and McDonald, 1995; Alexopoulos *et al.*, 1997b; Steffens and Krishnan, 1998). The VD hypothesis originated from the finding that patients with late-onset depression (LOD) had higher rates of hyperintensities on T2-weighted brain magnetic resonance imaging (MRI) than patients with early-onset depression (EOD) (Hickie *et al.*, 1995; Salloway *et al.*, 1996; Krishnan *et al.*, 1997a). It was further observed that patients with LOD and MRI hyperintensities demonstrated greater neuropsychological impairment than patients with EOD (Lesser *et al.*, 1996; Salloway *et al.*, 1996; Alexopoulos *et al.*, 1997c). Greater severity of MRI hyperintensities was also associated with poor response to treatment (Hickie *et al.*, 1995). Therefore, a coherent theory of VD emerged (Krishnan and McDonald, 1995; Alexopoulos *et al.*, 1997a, 1997c; Krishnan *et al.*, 1997b; Steffens and Krishnan, 1998) in which LOD was seen as a consequence of structural damage to corticostriatal circuits due to cerebrovascular disease, which led to executive dysfunction (ED) and poor antidepressant treatment response (see Figure 1).

The VD hypothesis proposes that cerebrovascular disease may predispose, precipitate, or perpetuate

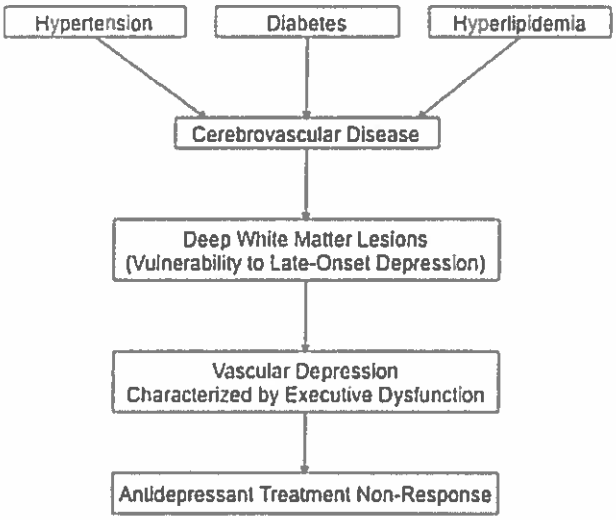

Figure 1 A schematic diagram of the vascular depression hypothesis (based on Krishnan and McDonald, 1995).

some geriatric depressive syndromes (Alexopoulos *et al.*, 1997a). As far as we know, personality traits (e.g., the Big Five factors) are not included in this model as a predisposing factor in the development of VD. Indeed, Sneed *et al.* (2007a) showed that neuroticism levels were lower among women with LOD than with EOD. However, these findings do not obviate the possibility that there are predisposing biological or genetic factors that are additional determinants of VD. In fact, there may be a strong genetic influence in the development of white matter hyperintensities (WMH) in the elderly. Heritability of WMH has been estimated to be between 55 and 80% (Carmelli *et al.*, 2002; Atwood *et al.*, 2004; Turner *et al.*, 2004; Assareh *et al.*, 2010).

There is considerable evidence that an ischemic cerebrovascular disease process is responsible for excessive deep WMH (DWMH) (Thomas *et al.*, 2000, 2002, 2003). For example, all DWMH in an elderly depressed group were ischemic in origin as compared with a third of those in an age-matched control group (Thomas *et al.*, 2002). Another study found a significant increase in ICAM-1 (a vascular marker of inflammation) in the deep white matter of the depressed group (compared to normal controls), supporting the hypothesis that DWMH are ischemia-induced (Thomas *et al.*, 2003).

Although it appears that there is an ischemic basis underlying DWMH, the mechanism underlying the ischemia is less clear although points to poor endothelial functioning and atherosclerosis (Tiemeier *et al.*, 2004; Paranthaman *et al.*, 2010). For example, one study found that depressed older adults had impaired endothelial function and more atherosclerosis when compared to controls (Paranthaman *et al.*, 2010). However, there has been recent interest in cerebral auto-regulation and regulation of blood pressure in relation to hyperintensities. Changes in autoregulation may be another age-associated change that leads to WMH in addition to atherosclerosis (Richardson *et al.*, 2009; Brickman *et al.*, 2010).

Enthusiasm for the construct of VD led a number of researchers to propose diagnostic criteria to define the subtype (Alexopoulos *et al.*, 1997b, 2002b; Steffens and Krishnan 1998; Alexopoulos, 2001; Krishnan *et al.*, 2004), though criteria have not always been consistent. Lack of consensus on criteria makes it difficult to interpret discrepant findings across studies (Sneed *et al.*, 2006). For instance, Sheline *et al.* (2010) showed that neuropsychological test performance and MRI hyperintensities predicted depression symptom severity over a 12-week course of treatment in LLD. However, the criteria used to define VD differed from other definitions used previously (Krishnan *et al.*, 1997a; Krishnan *et al.*, 2004; Sneed *et al.*, 2008). Because we do not know to what degree the presumably different patient groups overlap, there is no way to evaluate discrepant findings. To address this problem, Sneed *et al.* (2008) used data from two, large clinical samples of late-life depressed patients and showed that the vascular group, defined by a high probability of having MRI hyperintensities (deep white matter and periventricular), ED, and late age-at-onset, was most accurately identified by DWMH. Not only do these findings provide the first empirical evidence that VD is a unique subtype in late life but also provide the first empirically based diagnostic criteria for the illness.

Although there has been support for the validity of MRI-defined VD, a number of important substantive and methodological questions remain. For example, is it the size of each hyperintensity, total volume, location of DWMH or some combination of these factors that defines the syndrome? The definition of MRI-defined VD depends on the validity and reliability of the measurement of DWMH, which is almost never discussed in the VD literature. For example, what is the relationship between qualitative and quantitative measures of hyperintensities and what are their strengths and weaknesses? Furthermore, poor response to antidepressant treatment has been associated with one or more aspects of MRI-defined VD (e.g., hyperintensity load, ED, etc.). What is the relationship among hyperintensity severity, ED, and antidepressant treatment outcome? In what follows, we review the literature that bears on these questions in order to further elucidate MRI-defined VD.

Lesion location, ED, and MRI-defined VD

First, there is strong evidence that MRI hyperintensities are over-represented among the late-life depressed compared to age-matched controls. Studies have documented clinical and/or neuro-imaging evidence of cerebrovascular irregularities in LLD. In particular, when compared with age-matched controls, high rates of abnormality have been consistently observed in MRI of elderly patients with depression (Coffey *et al.*, 1993; Fujikawa *et al.*, 1993; Krishnan, 1993; Hickie *et al.*, 1995; Lesser *et al.*, 1996).

DWMH are not only associated with elderly depression, but also with late depression onset. Patients with LOD (onset after age 50) have greater DWMH than those with EOD (Steffens and Krishnan, 1998). Others have shown that patients with onset after age 60 tend to have increased DWMH as compared with age-matched patients with EOD (O'Brien *et al.*, 1996; Salloway *et al.*, 1996; de Groot *et al.*, 2000). One study found that 50% of late-onset depressed patients (age of onset >65) had severe DWMH (grade 3 on the Fazekas modified Coffey rating scale) compared to 20% of early onset depressed patients and 9.5% of age-matched controls (O'Brien *et al.*, 1996). In a systematic review, Herrmann *et al.* (2007) found that the odds of having DWMH are 4.33 times greater in LOD than EOD. Finally, in a population-based study (de Groot *et al.*, 2000), the likelihood of being diagnosed with LOD (age of onset >60) was 3.4 times more likely if MRI demonstrated severe DWMH (upper quartile) as opposed to mild or no evidence of hyperintensities.

There is evidence to suggest that DWMH are more strongly associated with depressive symptoms than periventricular hyperintensities (PVH). DWMH, and not PVH, were significantly associated with depressive symptoms in a sample of elderly depressed patients (Krishnan *et al.*, 2006). Similarly, in a sample of community-dwelling elderly individuals, DWMH, but not PVH, were associated with depressive symptoms (Nebes *et al.*, 2001). However, not all studies agree (Idaka *et al.*, 1996).

DWMH appear to be over-represented in anterior brain regions (Firbank *et al.*, 2004; Greenwald *et al.*, 1998). Elderly depressed subjects have significantly greater WMH volume in frontal areas compared to controls (Firbank *et al.*, 2004). For example, left frontal DWMH volume significantly predicted depressed group membership in a mixed sample of depressed and non-depressed older adults (Greenwald *et al.*, 1998). Another study found an association between age and DWMH in bilateral frontal regions in patients with LLD, but not in control subjects (Taylor *et al.*, 2003a). Diffusion tensor imaging studies in LLD have found markers of decreased white matter coherence (i.e., reduced fractional anisotropy (FA)) in frontal and temporal lobes (Taylor *et al.*, 2004).

DWMH in LLD may disrupt frontal-subcortical circuits integral to emotion regulation and executive functioning (Alexopoulos *et al.*, 1997b; Alexopoulos, 2001, 2002). For example, the presence and severity of anterior WMH volume has been negatively associated with right caudate (deep gray matter) volume in LLD (Hannestad *et al.*, 2006). Neuroimaging studies have also reported increased orbitofrontal lesion density in patients with LLD (MacFall *et al.*, 2001) and a negative association between WMH severity and orbitofrontal cortex volume (Taylor *et al.*, 2007). MRI of elderly depressed subjects showed decreased volume in the orbitofrontal cortex (Lai *et al.*, 2000; Taylor *et al.*, 2007), subcortical structures (i.e., basal ganglia and hippocampus) (Artero *et al.*, 2004), and gray and white matter of the anterior cingulate cortex (Hannestad *et al.*, 2006). Further, elderly depressed subjects had greater microstructural abnormalities (reduced FA) than controls in white matter lateral to the anterior cingulate cortex and in bilateral superior and left middle frontal gyri of the dorsolateral prefrontal cortex (Bae *et al.*, 2006). Finally, there is an inverse correlation between FA values of inferior frontal cortex white matter (including the medial orbital prefrontal region) and severity of depression (Nobuhara *et al.*, 2006). These findings are largely specific to deep white matter and suggest that frontal-subcortical circuits are compromised in LLD.

Abnormalities in frontal-subcortical circuits are associated with ED in LLD. Perseverative errors on the Benton Visual Retention Test were negatively associated with left orbitofrontal volume in LLD (Steffens *et al.*, 2003). Furthermore, disruption of those tracks integral to ED results in poor antidepressant treatment response. For example, markers of reduced white matter microstructure (reduced FA) of frontal-subcortical limbic regions, including prefrontal, insular, and parahippocampal regions and white matter lateral to the anterior and posterior cingulate cortex, were associated with poor response inhibition (as measured by the Stroop) in elderly depressed patients (Murphy *et al.*, 2007). This observation suggests that abnormalities within frontal-subcortical pathways contribute to the presence of ED in LLD, which in turn result in poor antidepressant treatment response. Although consistent with the VD hypothesis, it is unclear whether reduced FA values reflect underlying microvascular ischemia as other causes of reduced FA values are possible (e.g., neurodevelopmental process).

Methodological issues

There are many important methodological issues that bear directly on the validity of establishing MRI-defined VD as a distinct diagnostic subtype. Historically, MRI hyperintensities have been graded visually for severity using visual rating scales including the Fazekas modified Coffey rating scale, the Scheltens rating scale, Boyko Pathology Rating Scale, and Virchow–Robin spaces. The Fazekas modified Coffey rating scale (Coffey *et al.*, 1990) in particular has been used extensively in VD research (Krishnan *et al.*, 1997a; Krishnan *et al.*, 2004; Sneed *et al.*, 2007b, 2008). Virchow–Robin spaces, which are perivascular spaces that may indicate cerebral microvascular disease when abnormally dilated (Patankar *et al.*, 2005; Rouhl *et al.*, 2008) have also been important in the assessment of white matter lesion load in LLD (Paranthaman *et al.*, 2010). Visual ratings are of lesion severity only, though some scales like the Scheltens include ratings of lesion size. Benefits for visual rating scales include the ability of expert raters to use clinical judgment to evaluate the presence and distribution of lesions and discriminate meaningful patterns (e.g., WMH regions) from noise. Nevertheless, visual ratings are not able to quantify the volume of lesion load, which would represent a more quantitative index of lesion severity. They are time consuming, are not realistic for large datasets, and rely on clinical judgment, which raises issues of inter-rater reliability and validity.

Fully automated segmentation techniques obviate the inter-rater reliability problem because quantification of lesions is standardized and requires little user intervention. Other advantages include the generation of quantitative data and the ability to analyze large data sets quickly. Because of these advantages, automated methods are potentially superior to visual rating scales for quantifying signal hyperintensities on MRI. Indeed, visual ratings may be less sensitive than volumetric assessments in distinguishing between clinical groups because of potential ceiling effects and poor discrimination of absolute lesion volumes (van Straaten *et al.*, 2006). However, automated methods require computational sophistication, proper software, and a certain amount of user intervention (e.g., troubleshooting). Fully automated approaches also raise questions regarding validity because radiological artifacts may interfere with segmentation of MRI hyperintensities or with steps required to perform regional analyses. For example, automated segmentation techniques rely on the brightness of adjacent pixels to identify lesion boundaries, leading to a potential problem in distinguishing between pathological lesions and anatomical structures that are normally hyperintense on T2 FLAIR images (e.g., pyramidal tracts and hippocampus). The validity of MRI-defined VD, therefore, depends on the reliability and validity of the rating technique, which to our knowledge has not been fully established.

Another critical issue is how we define deep white, periventricular, and subcortical gray matter lesions. For example, subcortical ischemic disease can involve white or gray matter. Therefore, it is important to refer to subcortical ischemic disease as lesions possibly involving both white matter and deep gray nuclei structures. WMH may be considered 'periventricular' if they are distributed within a certain distance from the walls of the lateral ventricles or remain contiguous throughout their distribution. Clear criteria need to be operationalized so they can be applied consistently across datasets.

It is important to note that many primary care and community-based studies have not found differences in vascular risk factor burden between people with LLD and age-matched controls (Lyness *et al.*, 1998, 1999; Kim *et al.*, 2004; Naarding *et al.*, 2007). One reason these findings differ from hospital-based research may be their use of clinical measures of vascular risk that lack the sensitivity of MRI to detect cerebrovascular disease. Although this raises questions about the VD construct, it also points to the importance of using MRI itself to define the subtype.

Clinical characteristics, antidepressant treatment, and long-term outcome

If we take MRI evidence of hyperintensities to define the illness, we can begin to characterize the clinical presentation of MRI-defined VD. For instance, its clinical profile may be characterized by psychomotor retardation and lack of insight (Hickie *et al.*, 1995; Alexopoulos *et al.*, 1997c; Krishnan *et al.*, 2004) and associated with a low rate of family history of affective disorder (Hickie *et al.*, 1995; Krishnan *et al.*, 2004). Although patients with MRI-defined VD may have a low rate of affective disorder in their families, it is reasonable to hypothesize that patients at risk for MRI-defined VD may have a high rate of family history of vascular risk factors, though a clear pattern has not emerged in the literature (Kales *et al.*, 2005).

With regard to treatment outcome, a number of studies have shown that MRI signal hyperintensities predict poor antidepressant treatment response (Hickie *et al.*, 1995; Simpson *et al.*, 1998; Alexopoulos *et al.*, 2002a, 2008; Taylor *et al.*, 2003b; Navarro *et al.*,

2004; Patankar *et al.*, 2007; Gunning-Dixon *et al.*, 2010), though not all studies agree (Krishnan *et al.*, 1998; Salloway *et al.*, 2002; Janssen *et al.*, 2007; Sneed *et al.*, 2007b). In a recent study, elderly depressed patients who failed to remit following treatment with antidepressant medication had significantly greater MRI signal hyperintensity burden than both patients who remitted and elderly comparison subjects (Gunning-Dixon *et al.*, 2010), providing further support for the relationship between hyperintensity severity and antidepressant treatment response.

Although there is not a one-to-one relationship between ED and microvascular ischemic lesions, the two are often associated (Steffens *et al.*, 2003; Murphy *et al.*, 2007), included together as core features of the diagnostic criteria for VD (Alexopoulos *et al.*, 1997a; Krishnan *et al.*, 1997a), and may even define the same patient population (Kim *et al.*, in press; Sneed and Culang-Reinlieb, in press). Not surprisingly, research indicates that ED also predicts poor antidepressant treatment response and increased risk of relapse in LLD (Kalayam and Alexopoulos 1999; Alexopoulos *et al.*, 2000, 2005; Baldwin *et al.*, 2004; Murphy and Alexopoulos 2006; Sneed *et al.*, 2007b; Morimoto *et al.*, in press); however, not all studies agree (de Groot *et al.*, 1996; Butters *et al.*, 2004; Saghafi *et al.*, 2007). One study examined the predictive utility of all three diagnostic criteria for VD (i.e., age of onset, ED, and MRI hyperintensity burden) on antidepressant treatment response in depressed patients age 75 and over and found that only ED predicted poor response (Sneed *et al.*, 2007b).

Based on these findings it is likely that patients with VD may not respond as well to traditional antidepressant medication as non-VD patients. Alternative treatments, however, are beginning to emerge. For example, preliminary findings suggest that rTMS may be effective (Fabre *et al.*, 2004; Narushima *et al.*, 2010). In one randomized controlled trial of rTMS in the treatment of VD, active rTMS led to a significantly greater reduction of depressive symptoms when compared to sham stimulation (Fabre *et al.*, 2004). Problem-solving therapy may also be effective in the treatment of MRI-defined VD as preliminary evidence shows that it may be effective in patients with ED (Alexopoulos *et al.*, 2003; Kiosses *et al.*, 2010).

The course of MRI-defined VD remains largely unknown. Cerebrovascular disease is a progressive illness, which should have implications for long-term outcome. Depressed elderly patients who achieved and sustained remission after two years of naturalistic treatment and follow-up showed less progression of WMH volume than depressed patients who did not achieve or sustain remission (Taylor *et al.*, 2003a). These results suggest that progression of WMH can have a negative impact on treatment outcome and sustained remission in geriatric depression. If WMH represent an ongoing pathological vascular process then an intervention that increases perfusion and/or protects against reperfusion injury may be particularly effective, leading to better acute treatment outcomes and long-term prognosis. In fact, augmentation of antidepressant medication with Nimodipine (a calcium channel blocker used to treat hemorrhage-induced vasospasm) in the treatment of VD led to a greater and more rapid improvement in depressive symptomatology, lower rates of recurrence, and a higher rate of full remission when compared to those patients on antidepressant medication alone (Taragano *et al.*, 2001, 2005).

Conclusion

As is evident from this review, there is increasing evidence for MRI-defined VD to be considered as a distinct diagnostic subtype. It has a consistent theoretical basis and growing empirical support. However, the field must overcome significant challenges before it can recognize MRI-defined VD as a valid diagnostic entity. Chief among these challenges is demonstrating a causal link between cerebrovascular disease and depression, but this is a difficult hypothesis to test directly. In this regard, it is important to note that while WMH are highly prevalent among older adults, only a small percentage seem to develop LLD (Debette and Markus, 2010; Wallin and Fladby, 2010) and that older adults can have new onset depression in the absence of significant white matter disease. These observations suggest that cerebrovascular disease may be one component of the depressive syndrome in older adults but that it is neither sufficient nor necessary to cause depression. Another important challenge is establishing valid diagnostic criteria because, as has been previously discussed (Steffens, 2004; Alexopoulos, 2006; Sneed *et al.*, 2006; Taylor *et al.*, 2006; Sneed *et al.*, 2008), it is difficult to compare findings across studies in the absence of validated criteria.

MRI-defined VD must be understood in the context of other late-life disorders. It is possible that rather than representing a distinct diagnosis, MRI-defined VD may only be a prodrome for later dementia (Schweitzer *et al.*, 2002). In fact, the rate of conversion to dementia in patients with cognitive impairment and LLD is much higher than the rate of conversion in patients with cognitive impairment alone (Modrego

and Ferrandez, 2004). MRI-defined VD may therefore fall on a continuum consisting of vascular disease, VD, post-stroke depression, and vascular dementia (Sneed *et al.*, 2008). Another possibility is that VD is part of a larger category of geriatric syndromes that result from frontal-subcortical dysfunction (Pugh and Lipsitz, 2002). Traditionally, research on VD begins with patients who have a diagnosis of major depression. However, it has not been established that the mood disorder associated with cerebrovascular disease is restricted to major depression (Sneed *et al.*, 2008). Depression may be one among many manifestations of underlying cerebrovascular disease. For example, patients with damage to frontal-subcortical circuits might also present with vascular dementia, gait disturbance, or urinary incontinence with or without depression (Pugh and Lipsitz, 2002). A better understanding of the course of MRI-defined VD is needed in order to differentiate it from other late-life disorders and establish the diagnosis as a unique entity.

What are the implications MRI-defined VD in clinical practice? Late-onset depression could be used as a proxy for the illness because it circumvents the need for MRI and/or neuropsychological testing. However, it suffers from both the faulty assumption that people with EOD cannot have a VD in late-life as well as psychometric problems that limit its utility (Alexopoulos, 2006; Sneed *et al.*, 2006, 2008). Moreover, there is no reason to limit MRI-defined VD to late life, especially in populations that have high rates of vascular risk factors. Executive dysfunction could also be used as a proxy for MRI-defined VD and there are several tests of ED that could be accurately administered in a short period of time. The critical issue here is not the practicality of assessment but of interpretation. Moreover, ED is not specific to any one particular illness, and therefore, is a poor proxy on conceptual grounds.

Although MRI is an expensive and time-consuming test, depression is a debilitating, and in some cases, life-threatening disorder that deserves state-of-the-art clinical treatment. If it turns out that patients with MRI-defined VD do not respond to traditional antidepressant medication, then the use MRI as a diagnostic tool may save valuable time and resources because alternative treatments such as problem solving therapy could be initially recommended instead (Alexopoulos *et al.*, 2003; Kiosses *et al.*, 2010). This is all the more important because antidepressant non-response in late life may be associated with cognitive decline (Culang *et al.*, 2009). Therefore, it is possible that the expense is not only justified but may be necessary for good clinical practice.

Key Points

- Despite considerable data supporting the validity of MRI-defined vascular depression, there are a number of critical issues that remain, including establishing a causal relationship between cerebrovascular disease and late-life depression, establishing consistent diagnostic criteria, determining the importance of lesion type and location, and understanding the course of the disorder.

Conflict of interest

None declared.

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