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Preliminary communication

MRI signal hyperintensities and failure to remit following antidepressant treatment

Joel R. Sneed [a,b,g,h,*], Michelle E. Culang-Reinlieb [b], Adam M. Brickman [c,d], Faith M. Gunning-Dixon [e], Lauren Johnert [b], Ernst Garcon [f], Steven P. Roose [g,h]

[a] Queens College, City University of New York, Department of Psychology, United States
[b] The Graduate Center, City University of New York, United States
[c] Taub Institute for Research on Alzheimer's Disease and the Aging Brain, G.H. Sergievsky Center, Columbia University, United States
[d] Department of Neurology, College of Physicians and Surgeons, Columbia University, United States
[e] Weill Medical College of Cornell University, United States
[f] Department of Radiology, Columbia University Medical Center, United States
[g] Department of Psychiatry, Columbia University, United States
[h] New York State Psychiatric Institute, United States

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ABSTRACT

Background: MRI signal hyperintensities predict poor remission to antidepressant treatment. Previous studies using volumetrics in outpatient samples have relied on total lesion volume. The purpose of this study was to test whether remission from geriatric depression depends on lesion volume by region of interest (ROI).

Method: Thirty-eight patients received baseline MRIs as part of a larger 12-week, randomized clinical trial comparing sertraline and nortriptyline in the treatment of late-life depression. MRIcro was used to quantify MRI-hyperintensity volume into total hyperintensity, deep white matter hyperintensity (DWMH), and periventricular hyperintensity (PVH) volumes. High versus low total, DWMH, and PVH volumes were defined based on the highest quartile of their respective distributions. Remission from depression was defined as a 24-item Hamilton Rating Scale for Depression score ≤ 7 for two consecutive weeks.

Results: Patients classified as having high DWMH were 7.14 times more likely not to remit following antidepressant treatment compared to patients classified as having low DWMH ($p = 0.02$). Similar odds ratios were obtained for PVH (OR = 4.17, $p = 0.16$) and total volumes (OR = 5.00, $p = 0.05$). Importantly, adjusting for age did not change the magnitude of these effects.

Limitations: A small and predominantly White sample.

Conclusions: This is the first study to test whether remission from geriatric depression depends on lesion volume by ROI in an outpatient sample. The pattern of remission rates and odds ratios was similar when patients were classified as having high DWMH, PVH or total volume suggesting that lesion location may not be critical.

1. Introduction

MRI signal hyperintensities are common in late-life depression (LLD). When compared with age-matched controls, high rates of MRI abnormalities have been consistently observed in patients with LLD (Coffey et al., 1993; Fujikawa et al., 1993; Hickie et al., 1995; Krishnan, 1993; Lesser et al., 1996). MRI

* Corresponding author at: Department of Psychology, Queens College of the City University of New York, 65-30 Kissena Blvd., NSB A338, Queens, NY 11367, United States.
E-mail address: joel.sneed@qc.cuny.edu (J.R. Sneed).

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hyperintensities in LLD appear to be overrepresented in frontal and subcortical regions (Firbank et al., 2004; Greenwald et al., 1998; O'Brien et al., 1996; Taylor et al., 2003a), are associated with cognitive deficits (Kramer-Ginsberg et al., 1999; Lesser et al., 1996; Potter et al., 2007), and have been hypothesized to form the basis for vascular depression in late-life (Alexopoulos et al., 1997a, 1997b; Krishnan and McDonald, 1995; Krishnan et al., 1997; Steffens and Krishnan, 1998); that is, depression resulting from structural damage to corticostriatal circuits due to cerebrovascular disease that is characterized by executive dysfunction and poor antidepressant treatment response (Culang-Reinlieb et al., 2010).

Patients with LLD characterized by significant MRI signal hyperintensities have been shown to respond poorly to antidepressant treatment (Alexopoulos et al., 2002, 2008; Hickie et al., 1995; Navarro et al., 2004; Patankar et al., 2007; Simpson et al., 1998; Taylor et al., 2003b). For example, the sum of severity ratings across three brain areas (deep white matter, periventricular, and subcortical nuclei) based on a visual rating scale of MRI signal hyperintensities predicted depression symptom severity after 12 weeks of antidepressant treatment (Sheline et al., 2010). In another recent study, patients who failed to remit following treatment with antidepressant medication had significantly greater MRI signal hyperintensity burden compared to both patients who remitted and elderly comparison subjects using total lesion volume based on a semi-automated lesion quantification method (Gunning-Dixon et al., 2010).

However, not all studies agree (Janssen et al., 2007; Krishnan et al., 1998; Salloway et al., 2002b; Sneed et al., 2007). One study examined the predictive utility of age of onset, executive dysfunction, and MRI hyperintensity burden on antidepressant treatment response in depressed patients aged 75 and over and found that MRI hyperintensity severity did not predict poor response (Sneed et al., 2007). Similarly, a placebo-controlled trial of sertraline in older depressed outpatients found no association between MRI hyperintensities and acute treatment response to antidepressant medication (Salloway et al., 2002a). However, all of these studies have relied on either visual rating scales of lesion severity (Hickie et al., 1995; Navarro et al., 2004; Simpson et al., 1998; Sneed et al., 2007; Taylor et al., 2003a) or semi-automated methods to calculate total lesion volume (Gunning-Dixon et al., 2010; Sheline et al., 2010).

Only one study has attempted to decompose total volume into anatomically separate regions of interest to determine the relationship between volume of lesion location and outcome (Janssen et al., 2007). This 12-week controlled trial of venlafaxine or nortriptyline did not find an association between location and outcome but was conducted in depressed geriatric inpatients only. Therefore, the specificity of lesion location hypothesis has not been tested. This is interesting considering 1) the predictions based on the vascular depression hypothesis, 2) differences in the pathophysiology of deep white matter hyperintensities (DWMH) and periventricular hyperintensities (PVH) (Thomas et al., 2002a, 2002b, 2003), and 3) DWMH are more strongly associated with depressive symptoms in late-life than PVH (Krishnan et al., 2006; Nebes et al., 2001).

The purpose of this study is to examine the relationship between lesion volume location (as well as total volume) and remission from depression following antidepressant treatment. To address this issue, we use data from a 12-week, randomized, double-blind study of depressed older adult outpatients treated with sertraline or nortriptyline. To our knowledge, this is the first attempt to test the specificity of lesion volume location, which is important because lesion volume ratings are a more sensitive indicator of cerebrovascular disease than severity ratings (Gunning-Dixon et al., 2010). We hypothesized based on the vascular depression hypothesis that there would be a significant association between non-remission and high DWMH and total lesion volume but not PVH volume.

2. Methods

2.1. Participants

Thirty-eight patients meeting DSM-IV criteria for MDD of the melancholic or non-melancholic subtype received MRIs of the brain as part of a larger (N = 112) double-blind, randomized, 12-week clinical trial of nortriptyline and sertraline. Patients were recruited by radio and newspaper advertisements and/or through referral from other physicians to our university-based geriatric psychiatry clinic. At the initial visit, a comprehensive psychiatric evaluation, including a Structured Clinical Interview for DSM-IV, 24-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960), a Mini-Mental State Examination (MMSE) (Folstein et al., 1975), and a medical history was performed. If the patient met inclusion criteria and signed informed consent, a physical examination, an electrocardiogram, complete blood count, chemistries, electrolytes, and thyroid panel were performed.

Inclusion criteria were 1) age ≥ 45; 2) unipolar depression, single or recurrent, nonpsychotic, by DSM-IV criteria; 3) HRSD ≥ 16 at the initial visit and at the end of 1 week of placebo; and 4) willing and able to give informed consent. Exclusion criteria were 1) history of or current psychotic disorder, or substance dependence within the past year (other than nicotine) by DSM-IV criteria; 2) judged to have a current suicide risk or serious suicide attempt within the past year; 3) patients with coronary artery disease (e.g., myocardial infarction, coronary artery bypass, angioplasty), or with positive history of angina or positive stress test; 4) QRS interval greater than 0.12 s or Qtc interval ≥ 46 ms; 5) treatment with coumadin, heparin, or type 1 antiarrhythmic medications; 6) diagnosis of narrow angle glaucoma; 7) MMSE score ≤ 24; 8) stroke, epilepsy or Parkinson's disease; 9) an acute, severe or unstable medical condition; 10) positive urine toxicology screen for drugs of abuse (e.g., amphetamine, barbiturates, cocaine, marijuana, methadone, methaqualone, opioids, PCP); and 11) treatment in the current episode of depression with either nortriptyline with a plasma level between 50 and 150 ng/ml, desipramine or imipramine at a plasma level of 250 ng/nl or greater for at least 4 weeks, or paroxetine 40 mg, fluoxetine 40 mg or sertraline 200 mg for at least 4 weeks. Patients were asked but not required to participate in an MRI study prior to medication treatment.

2.2. Treatment

Patients who met inclusion/exclusion criteria and signed informed consent were given a one week, single-blind, placebo lead-in. If patients still met inclusion/exclusion criteria at the end of the placebo lead-in, or their HRSD scores did not

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decrease by over 25%, they were randomized (stratified by the presence or absence of melancholia subtype) to treatment with either nortriptyline or sertraline.

Patients treated with sertraline received 50 mg for 1 week and then 100 mg for the next 4 weeks. If the patient did not meet criteria for response at 5 weeks, the dose was increased to 150 mg/day. If the patient did not show evidence of response by week 9, the dose was increased from 150 to 200 mg/day. Treatment with nortriptyline was calculated at 1 mg/kg. Then, 1/3 of that dose was given on days 1 through 3, 2/3 on days 3 through 6 and the full dose of medication was given on day 7. Plasma levels were drawn 7 days later and the dose of nortriptyline was adjusted so that the plasma level was within 80–120 ng. The participant was continued on nortriptyline for a total of 12 weeks. To make the different treatments comparable, blood was drawn for all participants regardless of medication group.

2.3. Remission

Participants were considered to be in remission if their last two observations on the HRSD-24 were 7 or below. Although conservative, evidence suggests that using remission criteria that are too high (e.g., HRSD ≤ 10) leads to increased rates of relapse (Kupfer, 2005). Therefore, we chose a stringent definition that is also consistent with a number of recent reports examining the relationship between MRI signal hyperintensities and antidepressant treatment response (Gunning-Dixon et al., 2010; Sheline et al., 2010).

2.4. MRI

Magnetic resonance imaging was obtained during the one week, placebo lead-in and acquired using a 1.5 Tesla G.E. Signa Advantage system. The following sequence of acquisitions was obtained: (1) T_1-weighted sagittal "scout" images, (2) T_2-weighted axial and coronal fast spin echo (FSE) sequences through the entire brain, (3) volumetric 3D T_1-weighted gradient echo images (3D FMSPGR) of the entire head, (4) fluid-attenuated inversion recovery (FLAIR) images, and (5) magnetization transfer (MT). For the purposes of this analysis, we used the FLAIR sequence with the following parameters; 36 contiguous 3 mm thick sections, TR 11,000 ms, TE 145 ms, TI 2600 ms, ETL 16, 256 × 192 matrix, 22 cm FOV, 1 NEX, and three interleaved 3 section acquisitions in the axial plane through periventricular and centrum semiovale white matter (scan time 8:48 min).

2.5. Image analysis

Quantification of MRI-hyperintensity volume (total and by ROI) used the MRIcro software (Rorden and Brett, 2000). It involved a three-step procedure (depicted in Fig. 1) that has been used in previous studies (Brickman et al., 2009, 2011; Gurol et al., 2006). In the first step, each image is visually inspected and a filter is applied based on an intensity threshold that labeled voxels appearing as hyperintense. The upper and lower boundaries of the filter are adjusted accordingly, based on visual inspection of labeled voxels on one or more axial slices. During the second step, three series of gross regions-of-interest (ROIs), corresponding to WMH in periventricular areas, WMH in deep cortical areas, and subcortical gray matter (SCG) hyperintensities, are manually traced on a slice-by-slice basis excluding non-WMH areas that are labeled in step 1 (e.g., dermal fat). During the third step, new images reflecting the intersection of voxels labeled in step 2 with the voxels labeled in step 1 are generated. That is, the labeled voxels that are common in step 1 and step 2 are isolated in step 3 to generate total WMH volumes for periventricular and deep cortical regions, respectively. In step 3, MRIcro provides volumes for the ROIs in cm^3, based on the number of labeled voxels and voxel dimensions. These ROIs correspond to Fazekas' modified Coffey Rating Scale for signal hyperintensities (Coffey et al., 1990). However, because the correlation between SCG hyperintensities and DWMH ($r = 0.87$) was extremely high, we did not include SCG lesion volume in the analyses.

The distinction between periventricular and DWMH is made visually following several rules set a priori and implemented on each axial slice. White matter hyperintensities that are contiguous to the lateral ventricles and extended to the deep white matter are classified as periventricular. If there is at least 1 pixel that separates hyperintense pixels between periventricular and deep areas so that there are two distinct contiguous groups, they are classified separately. Deep and periventricular volumes are calculated for the left and right cerebral hemispheres separately. Total periventricular and DWMH volumes are calculated by adding left and right hemisphere values together. Total volumes are derived by summing periventricular and deep values.

2.6. Statistical analyses

To test for differences at baseline in clinical and demographic characteristics between patients classified as remitters and non-remitters, t-tests and χ^2 tests of independence were used. To examine the relationship between remission and MRI hyperintensity volume, both in terms of total volume and by ROI (DWMH and PVH volumes), patients were classified as having 1) high total hyperintensity volume, 2) high DWMH volume, and 3) high PVH volume if their volume scores were in the highest quartile of the distribution, which were all very highly positively skewed justifying this approach. The relationship between remission rates and hyperintensity volume status was assessed using exact logistic regression, which permits the estimation of odds ratios in small samples. All analyses were evaluated at the 5% level.

3. Results

Table 1 presents baseline demographic and clinical characteristics of the MRI sample, remitters, and non-remitters. The average study participant was 66 years old and completed about 4 years of college. The sample consisted of 63% women, had an average age-at-onset of depression of 46.5, an average Cumulative Illness Rating Scale-Geriatrics of 3.3, and an average baseline depression severity of 24.32 on the 24-item HRSD and 4.3 on the CGI-Severity scale. There were no observed differences between remitters ($n = 10$) and non-remitters ($n = 28$) on any demographic or clinical characteristic variables.

Patients classified as having high DWMH were 7.14 times more likely not to remit following antidepressant treatment

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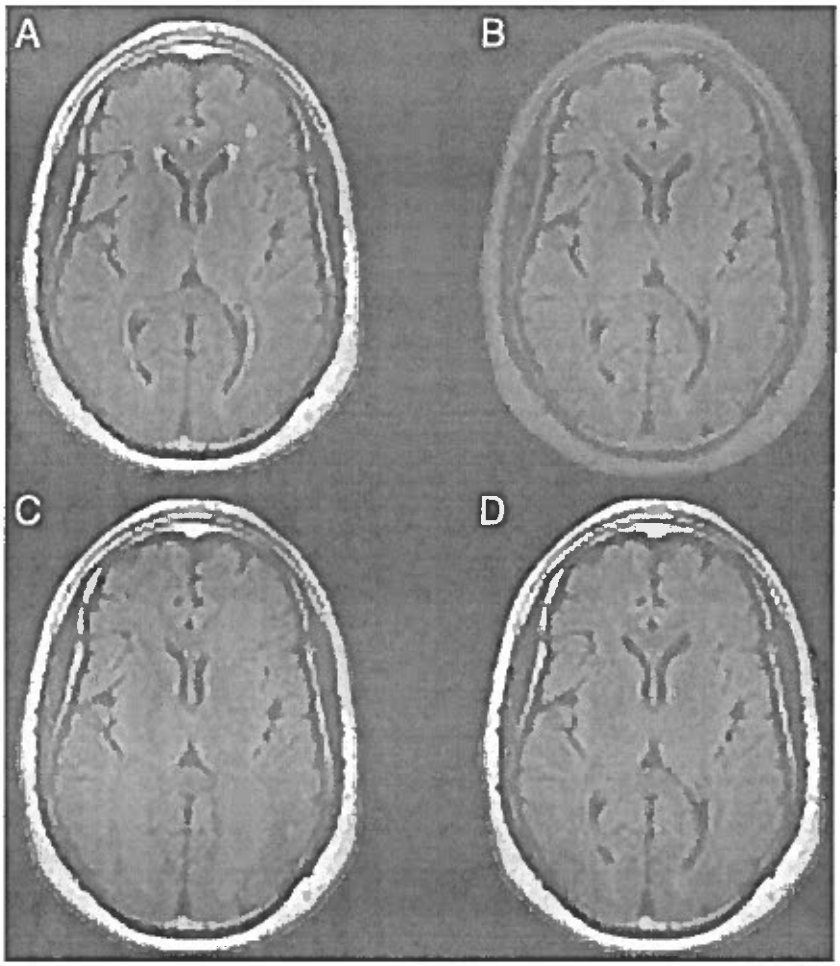

Fig. 1. (A) Original grayscale MRI axial FLAIR image from a representative subject; (B) region of interest (ROI) map created by semiautomatic intensity thresholding; (C) ROI map created by gross manual outlining of hyperintensities; (D) intersection of (B) and (C) yielding hyperintensity locations.

compared to patients classified as having low DWMH [odds ratio = 7.14 (1/.14), 95% CI 0–.79, p = .02]. Of the 10 patients classified as having high DWMH volume, none achieved remission. Similar odds ratios were obtained for PVH [odds ratio = 4.17 (1/.24), 95% CI .01–1.82, p = .16] and total hyperintensity volumes [odd ratio = 5.00 (1/.20), 95% CI 0–.1.12, p = .05]; 9 of 10 patients classified as having high PVH and all 8 patients classified as having high total volume did not remit. Importantly, adjusting for age did not change the magnitude of any of the effects.

Table 1
Clinical and demographic characteristics of the total sample, remitters, and non-remitters.

	Total sample (n = 38)	Remitters[a] (n = 10)	Non-remitters[b] (n = 28)
Age	66.0 (7.5)	64.7 (6.5)	66.5 (7.9)
Sex (% female)	63	50	68
Education	15.7 (2.9)	15.3 (3.7)	15. 8 (2.7)
MMSE	27.5 (2.9)	26.7 (4.1)	27.8 (2 3)
Baseline HDRS	24.5 (6.1)	22.0 (4.7)	25.4 (6.4)
Melancholic (%)	42	40	43
Age at onset	46.5 (22.5)	51.4 (18.7)	44.8 (23.7)
Recurrent MDD (%)	56	50	58
FH of psychiatric illness (%)	38	50	35
Sertraline (%)	45	30	50
CIRS-G	3.3 (2.1)	2.6 (1.4)	3.6 (2.2)
CGI-Severity	4.3 (1.1)	4.1 (0.60)	4.37 (1.2)

[a] HRSD ≤ 7 (last 2 consecutive observations).
[b] HRSD > 7 (last 2 consecutive observations).

4. Discussion

This is the first study to test whether volume of lesion location in addition to total volume predicts remission rates to antidepressant medication in an outpatient late-life depressed sample. We found that patients with high DWMH, PVH, and total lesion volumes were about four to seven times more likely not to remit following antidepressant treatment compared to patients classified as having low DWMH, PVH and total lesion volumes. Our findings converge with a growing literature documenting poor treatment response in patients with high hyperintensity volume (Alexopoulos et al., 2002, 2008; Hickie et al., 1995; Navarro et al., 2004; Patankar et al., 2007; Simpson et al., 1998; Taylor et al., 2003b) and build on previous studies that have relied on either visual rating scales of lesion severity (Hickie et al., 1995; Navarro et al., 2004; Simpson et al., 1998; Sneed et al., 2007; Taylor et al., 2003a) or semi-automated

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methods to calculate total lesion volume (Gunning-Dixon et al., 2010; Sheline et al., 2010).

This is somewhat surprising given the etiological and clinical distinctions that have been made between PVH and DWMH. For example, there is evidence to suggest that DWMH are more strongly associated with depressive symptoms than PVH (Krishnan et al., 2006; Nebes et al., 2001). Furthermore, the pathophysiology of DWMH in geriatric depression appears to be ischemic in origin (Thomas et al., 2002a) whereas the pathophysiology of PVH is less well-defined (Thomas et al., 2002b, 2003). Such differences between DWMH and PVH would presumably have implications for treatment response.

The findings support the vascular depression hypothesis in general in that patients with high lesion volume respond poorly to antidepressant treatment (Alexopoulos et al., 2002, 2008; Hickie et al., 1995; Navarro et al., 2004; Patankar et al., 2007; Simpson et al., 1998; Taylor et al., 2003b). However, they do not support the specificity of lesion location implied by the model. According to the model, cerebrovascular insufficiency in older persons leads to key changes in subcortical structures, which provide structural basis for late-onset affect disorders characterized by deficits in those functions dependent on intact corticostriatal connections (e.g., executive dysfunction) and poor response to antidepressant treatment (Culang-Reinlieb et al., 2010).

However, the distinction between DWMH and PVH may be somewhat arbitrary. Typically, in individuals with low burden, the WMH are adjacent to the lateral ventricles and progressively extend deeper in the cerebrum toward the cortex. While most classification schemes, including our own, rely on a distance threshold to distinguish between the two, when considered in three-dimensions it is evident that in most cases the distribution of the hyperintense signal is contiguous. While the regional distribution of WMH might have relevance in terms of the underlying pathology (Brickman et al., 2009), intensity distributions of abnormal signal on T_2-weighted MRI sequences, such as FLAIR, do not appear to vary by location and suggest interconnectivity of abnormal signal rather than a discrete topological distribution.

This study has several limitations. First was its small sample size, which prevented us from addressing a number of interesting questions including differences between melancholics and non-melancholics as well differences in medication assignment (i.e., sertraline or nortriptyline). This shortcoming is notable because, based on the post-stroke depression literature, patients with vascular depression may preferentially respond to tricyclic antidepressants as compared to selective serotonin reuptake inhibitors (Robinson et al., 2000). Another limitation was that the sample was predominantly White. This limitation is significant because vascular depression may be overrepresented among African-Americans; this subgroup has higher rates of cardiovascular disease risk factors (Geronimus et al., 2007; Kramer et al., 2004), stroke (Harris et al., 2005; Kissela et al., 2004), and vascular dementia (Kuller et al., 2005) than Whites.

5. Conclusion

The present study demonstrates that patients with high lesion volume fail to remit following treatment with antidepressant medication (both sertraline and nortriptyline). However, they also suggest that lesion location does not matter but rather it is total volume that is critical. While our findings support the vascular depression hypothesis in general they do not support the specificity of lesion location hypothesis based on the model. Our findings are consistent, however, with the contiguous nature of lesions seen as hyperintense on T_2-weighted FLAIR MRI images.

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Conflict of interest

SPR has received consultant fees from Medtronics and Orexigen. All other authors declare that they have no conflicts of interest.

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