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White Matter Hyperintensity Accumulation During Treatment of Late-Life Depression

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White matter hyperintensities (WMHs) have been shown to be associated with the development of late-life depression (LLD) and eventual treatment outcomes. This study sought to investigate longitudinal WMH changes in patients with LLD during a 12-week antidepressant treatment course. Forty-seven depressed elderly patients were included in this analysis. All depressed subjects started pharmacological treatment for depression shortly after a baseline magnetic resonance imaging (MRI) scan. At 12 weeks, patients underwent a follow-up MRI scan, and were categorized as either treatment remitters ($n=23$) or non-remitters ($n=24$). Among all patients, there was as a significant increase in WMHs over 12 weeks ($t(46)=2.36$, $P=0.02$). When patients were stratified by remission status, non-remitters demonstrated a significant increase in WMHs ($t(23)=2.17$, $P=0.04$), but this was not observed in remitters ($t(22)=1.09$, $P=0.29$). Other markers of brain integrity were also investigated including whole brain gray matter volume, hippocampal volume, and fractional anisotropy. No significant differences were observed in any of these markers during treatment, including when patients were stratified based on remission status. These results add to existing literature showing the association between WMH accumulation and LLD treatment outcomes. Moreover, this is the first study to demonstrate similar findings over a short interval (ie 12 weeks), which corresponds to the typical length of an antidepressant trial. These findings serve to highlight the acute interplay of cerebrovascular ischemic disease and LLD.

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INTRODUCTION

Among community-dwelling older adults, late-life depression (LLD) has been estimated to affect ~2% of patients based on strict diagnostic criteria (Beekman *et al*, 1999). Depression results in more years lived with a disability compared with any other disease, and also carries increased risks of suicide, medical comorbidities, and family caregiver burden (Casten *et al*, 1999; Garcia-Pena *et al*, 2013; Katon *et al*, 2010; Mulsant *et al*, 2006; Nelson *et al*, 2013). Unfortunately, LLD has a high treatment failure rate (ie 40–60%) with current first-line agents (Lebowitz *et al*, 1997). Furthermore, patients who eventually respond to treatment will likely take longer to do so (ie 8–12 weeks) compared with patients with depression during other stages of life (Reynolds and Kupfer, 1999). For these reasons, much of LLD neuroimaging-based research has sought to identify markers that may help decrease the interval between diagnosis and remission. Specifically, multiple groups have sought to establish the presence of any structural or functional imaging markers that could inform clinicians of a patient's likelihood of achieving remission with a given antidepressant trial (Aizenstein *et al*, 2014).

Many magnetic resonance imaging (MRI) studies have shown that LLD is associated with demyelinating lesions, which are seen as white matter hyperintensities (WMHs) on MRI (Chen *et al*, 2006; Firbank *et al*, 2012; Herrmann *et al*, 2008; Krishnan *et al*, 2004; Taylor *et al*, 2005, 2013). In older adults, the etiology of these lesions is largely thought to be related to ischemic disease, but other neuropathologic processes may also have a role. This view has been supported by research demonstrating WMH's association with cardiovascular risk factors and pathological markers of ischemia such as arteriosclerosis, vascular ectasia, infarction, and upregulation of ischemic cellular processes (Chimowitz *et al*, 1989; Debette *et al*, 2011; Thomas *et al*, 2002; van Dijk *et al*, 2008). Furthermore, one of the most salient models of depression in older adults is the vascular depression hypothesis, which suggests that cerebrovascular ischemic damage promotes depressive symptoms (Alexopoulos *et al*, 1997; Butters *et al*, 2008). The relationship between WMHs and the vascular depression hypothesis is further strengthened by studies demonstrating that WMHs are associated with treatment outcomes (Aizenstein *et al*, 2011; Firbank *et al*, 2007; Heiden *et al*, 2005; Taylor *et al*, 2014). However, as several other studies have failed to find the association between WMHs and depression, the vascular depression hypothesis is not universally accepted (Aizenstein *et al*, 2011;

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Dotson *et al*, 2013). The failure to find robust cross-sectional associations between cerebrovascular disease and LLD does not prove that WMH changes do not promote depression, but may suggest that the association with depression is weak given the large variability of WMHs across elderly individuals. Another possibility is that the relationship between WMHs and depression is related more to the accumulation of white matter lesions rather than their overall burden. That is, individuals undergoing active ischemic white matter changes may be more likely to develop depression, or have more difficulty responding to treatment compared with those with static amounts of WMHs.

Few studies have characterized WMH changes over time, and of those that have, only differences over multiple years have been assessed (Chen *et al*, 2006; Firbank *et al*, 2012; Rosano *et al*, 2005; Schmidt *et al*, 1999). It is possible that WMH changes in LLD patients are occurring over more acute intervals than has been previously studied, and furthermore, that these changes may impact patient treatment trajectories. Evidence for or against such an effect would help guide further refinement of the vascular depression hypothesis. For this reason, we sought to investigate these brain changes over 12 weeks, which is the standard treatment interval for patients with LLD. The principal hypothesis of this study was that significant differences in WMHs would be observed in LLD patients between treatment initiation and 12 weeks. Furthermore, we expected a divergence in our results based on remission status following treatment.

As LLD etiology is not likely solely attributable to a single factor, we also used this experimental design to assess other MRI markers of brain integrity, including fractional anisotropy of white matter, whole brain gray matter, and bilateral hippocampal volumes. Fractional anisotropy, a measure of microstructural integrity of the white matter, is intimately related to WMHs from an etiological perspective, and previous research has been able to demonstrate similar associations with treatment outcomes in LLD (Alexopoulos *et al*, 2002, 2008, 2010). Whole brain gray matter and bilateral hippocampal volumes are more representative of the interplay of atrophy and possible neurotoxicity in LLD (Andreescu *et al*, 2008). However, there is some evidence to suggest that WMHs can effect cerebral volumes in some limited neural structures (Hannestad *et al*, 2006; Taylor *et al*, 2007). For these reasons, as a secondary hypothesis we expected to find significant differences among these markers in LLD patients over the 12 weeks of antidepressant treatment. Again, it was anticipated that stratification by remission status would yield differential results.

MATERIALS AND METHODS

Study Design

Approval for this study was granted by the University of Pittsburgh Institutional Review Board. The study duration was 12 weeks, during which participants underwent an antidepressant treatment trial. MRIs were performed before starting medication ('baseline scan') and 3 months later ('follow-up scan'). Study participants were drawn from multiple open-label treatment studies of LLD at the University of Pittsburgh's Advanced Center for Interventions and Services Research for the Study of Late Life Mood Disorders. Comprehensive protocols for these studies are detailed elsewhere (Saghafi *et al*, 2007; University of Pittsburgh, National Institutes of Health, 2008, 2009, 2010). Briefly, patients were $\geqslant 60$ years old, and identified as suffering from major depression using the Structured Clinical Interview for DSM-IV disorders. A baseline depression severity of at least moderate intensity was ensured by requiring patients to have a score of $\geqslant 15$ on either the Hamilton Rating Scale for Depression (HRSD) or Montgomery-Asberg Depression Rating Scale (MADRS), depending on the parent study. To exclude patients with cognitive impairments, patients were administered a Mini-Mental State Exam (MMSE) and required to have a score >18. Patients were excluded if they had a clinical history of any bipolar disorder, psychotic disorder, or alcohol/drug abuse within the past 3 months. Finally, patients with contraindications to MRI were excluded. This included the presence of any retained paramagnetic material, weight >250 lbs, or claustrophobia. Patients were not excluded from this study based on prior antidepressant treatment nor was there a minimum antidepressant-free interval before enrolling.

As part of their respective treatment studies, patients received either escitalopram, duloxetine, or venlafaxine. Details regarding the administration and management of these medications were managed by the individual treatment studies. For patients receiving escitalopram, the starting dosage was 10 mg per day, and was titrated up to 20 mg per day based on clinical response. Patients receiving duloxetine began at 20 mg per day, which could be increased to 120 mg per day if necessary. Finally, patients receiving venlafaxine were titrated upwards from 37.5 mg to a maximum dose of 150–300 mg based on standard guidelines from the manufacturer. After patients underwent their follow-up scan at 12 weeks, they were classified as remitters if their HRSD score was $\leqslant 7$ or their MADRS score was $\leqslant 10$. Selection of remission thresholds was based on two independent linear regression analyses, which both demonstrated that an HRSD score of $\leqslant 7$ corresponds to a MADRS score of $\leqslant 10$ (Heo *et al*, 2007; Zimmerman *et al*, 2004). The former threshold was originally proposed by Frank *et al* (1991), and has since become the dominant cutoff for remission in depression research (Kupfer, 2005).

Image Acquisition and Analysis

MRIs were performed at the MR Research Center at the University of Pittsburgh with a 3 T scanner (Siemens, Berlin, Germany). A T2-weighted fluid attenuation inversion recovery (FLAIR) sequence was used for WMH measurements in the axial orientation. Relevant sequence parameters included slice thickness = 3 mm, number of slices = 48, acquisition matrix = 212×256 mm^2, voxel size = $1 \times 1 \times 3$ mm^3, repetition time (TR) = 9160 ms, echo time (TE) = 90 ms, inversion time (TI) = 2500 ms, and flip angle = 150°. WMHs were quantified with an automated method developed and validated by Wu *et al* (2006b). This method uses a fuzzy connectedness algorithm to automate WMH segmentation from T2-weighted FLAIR images. It then uses the John Hopkins University White Matter Atlas to automate the anatomic localization of WMHs using a demons-based

image registration (Wakana *et al*, 2004). The localized WMH voxel counts were divided by total brain volume voxel counts to yield normalized WMH (nWMH) values. This step was performed to control for differences in total brain volume among patients, as this value may impact the rate of WMH development. Non-nWMH values were also calculated by multiplying the WMH voxel counts by voxel size.

For gray matter and hippocampal volume measurements, a T1-weighted high-resolution magnetization-prepared rapid gradient echo (MPRAGE) sequence in the axial orientation was used. Imaging parameters included slice thickness = 1 mm, number of slices = 176, acquisition matrix = 224×256 mm^2, voxel size = $1 \times 1 \times 1$ mm^3, TR = 2300 ms, TE = 3430 ms, TI = 900 ms, and flip angle = 9°. Measures of whole brain gray matter and hippocampal volumes were extracted using Automated Labeling Pathway, a method we developed to implement Atlas-based segmentation of MR images. This is a semiautomated method that labels regions of interest on the high-resolution T1 image of each subject (Aizenstein *et al*, 2005; Rosano *et al*, 2005; Wu *et al*, 2006a). These values were both normalized by dividing by total intracranial volume. A diffusion tensor imaging sequence in the axial orientation was used to assess white matter microstructure. Images were acquired with the following parameters: slice thickness = 3 mm, number of slices = 40, acquisition matrix = 256×256 mm^2, voxel size = $2 \times 2 \times 3$ mm^3, TR = 5300 ms, TE = 88 ms, TI = 250 ms, and flip angle = 90°, diffusion directions = 12, diffusion values $b = 0$ s/mm^2 and $b = 1000$ s/mm^2, four repeats, and radial generalized autocalibrating partially parallel acquisitions (GRAPPA) = 2. Fractional anisotropy of 'normal-appearing' white matter was estimated with Tract-Based Spatial Statistics, part of the FSL software package (Analysis Group, Oxford, UK) (Jenkinson *et al*, 2012; Smith *et al*, 2006). WMHs were masked out of this analysis.

Statistical Analysis

After patients were categorized based on remission status, we performed statistical analysis of pertinent covariates comparing baseline characteristics between the groups. A two-sample Student's *t*-test was used to assess for significant differences between remitters and non-remitters with respect to age, MMSE, baseline depression rating scores, Cumulative Illness Rating Scale-Geriatric (CIRSG) vascular score, and antidepressant end dosage. A χ^2 test was performed to detect significant differences with respect to various dichotomized characteristics, including gender, depression onset (ie early- or late-onset LLD), anti-inflammatory medication use, and benzodiazepine use.

The nWMH values among all patients were compared between baseline and follow-up using a paired *t*-test to determine if WMHs changed over the treatment period. Patients were then stratified by remission status, and again a paired *t*-test was used to compare nWMH means between baseline and follow-up in each group. To assess for any differences in nWMH group means at baseline, a two-sample *t*-test was performed. Identical analyses were performed for normalized gray matter volumes, normalized hippocampal volumes, and fractional anisotropy. All statistical tests were two-tailed and considered statistically significant at an α-level < 0.05. Statistical analysis was performed using SPSS statistical software (IBM, Endicott, NY).

RESULTS

Of the 47 depressed subjects included in this protocol, 23 met the criteria for remission, whereas 24 were still depressed at follow-up according to their depression rating scores. In the analysis of baseline characteristics between remitters and non-remitters, the only significant differences observed were with respect to escitalopram and venlafaxine antidepressant end dosages ($t = 2.26$, d.f. = 15, $P = 0.04$; $t = 2.76$, d.f. = 25, $P = 0.01$), and proportion of patients with early- *vs* late-onset LLD ($\chi^2 = 5.25$, d.f. = 1, $P = 0.02$). Table 1 fully summarizes this analysis.

In assessing our primary hypothesis, we sought to determine whether among all patients there was a significant difference in nWMHs (ie WMH voxels/total brain voxels) between baseline and follow-up at 12 weeks. A significant increase in nWMHs ($t = 2.36$, d.f. = 46, $P = 0.02$) among all patients was observed. When the patient sample was stratified by remission status, non-remitters demonstrated a significant increase in nWMHs between baseline and follow-up ($t = 2.17$, d.f. = 23, $P = 0.04$), but this finding was not replicated in the remitters ($t = 1.09$, d.f. = 22, $P = 0.29$). These findings persisted even when the analysis was repeated with non-nWMH values. Finally, the baseline nWMHs were not significantly different between remitters and non-remitters ($t = 1.27$, d.f. = 28.13, $P = 0.10$). These results are summarized in Table 2 and Figure 1.

An exploratory analysis was also performed to identify any potential confounders between remission status and nWMHs. The factors antidepressant type, early- *vs* late-onset LLD (ie threshold of 60 years), current age, Cumulative Illness Rating Scale-Geriatric vascular score, anti-inflammatory medication use, and benzodiazepine use were selected as the most likely candidates to be associated with remission status and nWMHs. Patients were stratified based on each of these factors, and underwent paired *t*-tests comparing day 1 and week 12 nWMHs. This analysis revealed three of the above factors as differentially affecting accumulation of nWMHs. Stratification based on antidepressant type revealed that only escitalopram-treated patients significantly accumulated nWMHs ($t = 2.42$, d.f. = 15, $P = 0.03$). In the early/late-onset LLD stratification, the early-onset LLD patients demonstrated a significant increase in nWMH ($t = 2.93$, d.f. = 31, $P = 0.02$), whereas the late-onset LLD did not ($t = 0.77$, d.f. = 14, $P = 0.45$). Finally, stratification based on anti-inflammatory medication use revealed an increase in nWMHs only among patients who did not use these agents ($t = 2.62$, d.f. = 20, $P = 0.02$). As an additional step, patients within each of these significant subsamples were further stratified based on remission status. Within the escitalopram and early-onset LLD samples, only non-remitters demonstrated significant increases in nWMHs ($t = 2.45$, d.f. = 7, $P = 0.04$; $t = 2.18$, d.f. = 19, $P = 0.04$). A similar finding was observed in the sample of patients who did not use anti-inflammatory agents, but it was marginally nonsignificant ($t = 2.12$, d.f. = 13, $P = 0.054$). This exploratory analysis is comprehensively detailed in Table 3.

In addressing the study's secondary hypothesis, we analyzed the changes in whole brain gray matter volume, bilateral hippocampal volumes, and fractional anisotropy of normal-appearing white matter between baseline and follow-up. When each of these markers among all patients

Table 1 Patient Characteristics

	Remitters ($n=23$)	Non-remitters ($n=24$)	Statistic (t/χ^2)	*P*-value
Age (years)	68.0 (5.7)	66.8 (5.7)	−0.70 (t)	0.49
Gender (M/F)	9/14	6/18	1.08 (χ^2)	0.30
MMSE	28.6 (1.2)	28.75 (1.2)	0.53 (t)	0.60
HRSD baseline ($n=31$)	19.2 (3.0)	20.8 (4.1)	1.29 (t)	0.21
MADRS baseline ($n=16$)	26 (8.6)	25.8 (5.8)	−0.05 (t)	0.96
Depression onset (early/late)	12/11	20/4	5.25 (χ^2)	0.02[a]
Anti-inflammatory medication use (none/1+agent)	7/16	14/10	3.70 (χ^2)	0.54
Benzodiazepine use (none/1+agent)	15/8	10/14	2.62 (χ^2)	0.11
CIRSG vascular score (0–4)	1.8 (0.74)	1.6 (0.78)	−0.90 (t)	0.37
Antidepressant end dosage				
Escitalopram ($n=16$)	13.8 (5.2)	18.8 (3.5)	2.26 (t)	0.04[a]
Venlafaxine ($n=26$)	199.0 (60.0)	266.4 (59.2)	2.76 (t)	0.01[a]
Duloxetine ($n=5$)	60.0 (0)	90.0 (42.4)	0.63 (t)	0.57

Abbreviations: CIRSG, Cumulative Illness Rating Scale-Geriatric; HRSD, Hamilton Rating Scale for Depression; MADRS, Montgomery Asberg Depression Rating Scale; MMSE, Mini-Mental State Exam.
[a]Statistical significance. Data are represented as mean (SD), unless otherwise indicated.

Table 2 Change in White Matter Hyperintensities During Treatment

	Baseline	Follow-up	Mean difference (95% CI)	*t*-Score	d.f.	*P*-value
Normalized WMHs (%)						
Overall ($n=47$)	1.38×10^{-3} (1.89×10^{-3})	1.71×10^{-3} (2.36×10^{-3})	3.27×10^{-4} (4.76×10^{-5} to 6.07×10^{-4})	2.36	46	0.02[a]
Remitters ($n=23$)	1.03×10^{-3} (8.22×10^{-4})	1.23×10^{-3} (1.18×10^{-3})	2.03×10^{-4} (1.84×10^{-4} to 5.90×10^{-4})	1.09	22	0.29
Non-remitters ($n=24$)	1.72×10^{-3} (2.49×10^{-3})	2.17×10^{-3} (3.06×10^{-3})	4.47×10^{-4} (2.04×10^{-4} to 8.73×10^{-4})	2.17	23	0.04[a]
Non-normalized WMHs (cm^3)						
Overall ($n=47$)	0.56 (0.77)	0.68 (0.94)	0.12 (0.02 to 0.22)	2.45	46	0.02[a]
Remitters ($n=23$)	0.41 (0.30)	0.49 (0.45)	0.08 (−0.06 to 0.22)	1.19	22	0.25
Non-remitters ($n=24$)	0.71 (1.03)	0.87 (1.22)	0.16 (0.01 to 0.31)	2.22	23	0.04[a]

Abbreviations: d.f., degrees of freedom; WMH, normalized white matter hyperintensities.
[a]Statistical significance ($P<0.05$). Data are represented as mean (SD), unless otherwise indicated.

were compared between these time points, no significant differences were observed. Upon stratification by remission status, no significant differences were observed either. However, the data did demonstrate an increase in bilateral hippocampal volumes between baseline and follow-up among remitters, but this increase did not reach statistical significance ($t=-1.93$, d.f. $=22$, $P=0.07$). Finally, when comparing baseline gray matter volume, hippocampal volume, and fractional anisotropy between remitters and non-remitters, no significant differences were observed ($t=0.008$, d.f. $=45$, $P=0.99$; $t=-0.163$, d.f. $=45$, $P=0.87$; $t=-0.436$, d.f. $=45$, $P=0.67$). Table 4 summarizes these results.

DISCUSSION

This data suggests there is an increase in WMHs among depressed subjects during the 12-week treatment course, and that this effect is primarily driven by non-remitters. The primary implication of these findings is that an increase in WMHs over time may be associated with potentiation of depressive symptoms. The vascular depression hypothesis suggests that WMHs are a likely manifestation of subclinical cerebrovascular disease. This is supported by multiple studies linking WMHs with factors such as hypertension, tobacco use, and diabetes, which are all known contributors to both large and small vessel disease (Herrmann *et al*, 2008). It is thought that low-level cerebrovascular disease results in disruption of frontostriatal circuits, which are necessary for mood regulation (Alexopoulos *et al*, 1997; Lenze *et al*, 1999). Therefore, one possible interpretation of the association between WMH accumulation and non-remission is that the former represents further degradation of these neural pathways, which are critical to patient recovery. This hypothesis arises from a number of previous studies, which demonstrate that WMHs and microstructural abnormalities in specific frontostriatal circuit structures are associated with

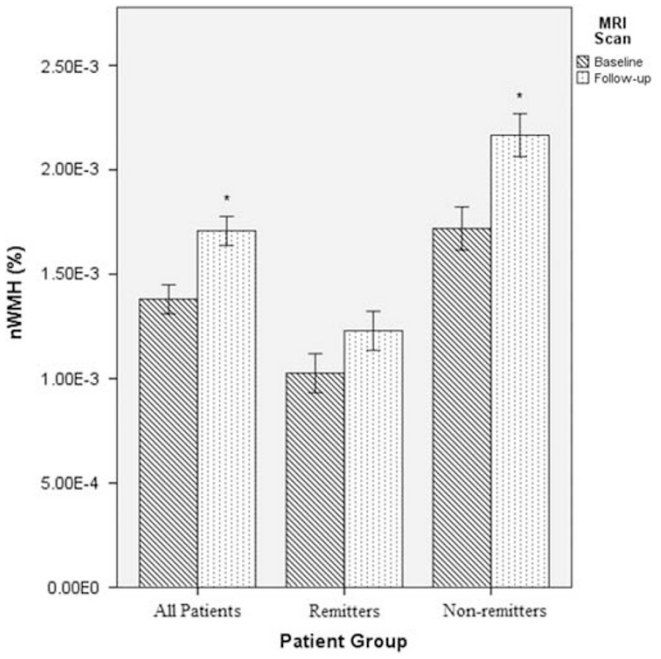

Figure 1 Change in normalized white matter hyperintensities (nWMH) during a 12-week antidepressant course. Patient results demonstrate significant nWMH increased among all patients and non-remitters. Data were corrected for between-subject variability to accurately visualize within-subject statistical design. Data were presented as mean ± SEM.

treatment outcomes in LLD (Alexopoulos *et al*, 2002, 2008, 2010; Taylor *et al*, 2014).

It is also a distinct possibility that this effect is bidirectional. That is, depression may promote the accumulation of WMHs, and perhaps these negative effects are mitigated when depression enters remission. The bidirectional nature of depression and white matter changes is described in recent reviews of vascular depression (Alexopoulos, 2005; Teper and O'Brien, 2008). Multiple explanations have been proposed for depression's effect on WMH development including depression-induced chronic hypothalamus–pituitary–adrenal (HPA) axis activation. Persistently elevated cortisol levels, as is seen in depression, is known to accelerate the formation of atherosclerotic plaques and promote vascular disease. Another suggested mechanism is the upregulation of inflammatory cytokines, which has been well documented in depressed patients. Evidence currently supports the role of these cytokines in mediating endothelial dysfunction, and they are also known to interact with the HPA axis, possibly amplifying this pathway (Teper et al, 2008). The existence of these and other plausible pathophysiological pathways indicates that the development of WMHs is likely multifactorial, and furthermore indicates that the bidirectional relationship between depression and WMHs is complex and currently incompletely characterized.

This study's exploratory analysis of possible confounders supports this understanding, as it reveals multiple factors beyond remission status, which affect accumulation of WMHs. These included antidepressant type, early- *vs* late-onset LLD, and anti-inflammatory use. Upon further substratification within these categories, it becomes clear that each of these factors association with WMHs is primarily driven by non-remitters. In the context of baseline comparisons of these factors between remitters and non-remitters, it appears that both escitalopram treatment and anti-inflammatory medication use themselves are not related to remission status, but instead may have divergent impacts upon WMHs among remitters and non-remitters (see Table 1). Specifically, escitalopram treatment and non-use of anti-inflammatory agents may result in accelerated WMH accumulation only among non-remitters. Although anti-inflammatory use can readily be understood to influence inflammatory and thrombotic pathways resulting in altered WMH development, escitalopram's effect on WMHs has a more nuanced interpretation. Selective serotonin reuptake inhibitors (SSRIs) such as escitalopram have been identified as potent disruptors of normal hemostasis as compared with other antidepressant classes with impairment in platelet aggregation and prolonged bleeding time, effects that may possibly inhibit thromboembolic events (Halperin and Reber, 2007). Conversely, it has been proposed that SSRIs stimulate vasoconstriction via serotonin receptors on vascular smooth muscle (Wu *et al*, 2011). Regardless of these seemingly contradictory effects on perfusion, these agents have been extensively associated with both cardiovascular disease and cerebrovascular events (Chen *et al*, 2008; Smoller *et al*, 2009; Weeke *et al*, 2012; Whang *et al*, 2009; Wu *et al*, 2011). The two studies that specifically examined the effect of SSRIs on WMHs both found an increase in WMHs among SSRI-treated patients, but only one demonstrated a statistically significant relationship (Grool *et al*, 2013; Steffens *et al*, 2008). From this information, it can be surmised that there may indeed be an effect of SSRIs on WMH accumulation, but further study is required to fully elucidate this relationship and also explore how serotonin-norepinephrine reuptake inhibitors (eg venlafaxine and duloxetine) may affect WMHs, for which data are currently lacking.

In contrast to antidepressant-type and anti-inflammatory medication use, which are only associated with WMH accumulation, early-onset LLD appears to be associated with both remission status and WMH accumulation according to the comparison of remitters/non-remitter characteristics and the exploratory analysis. Therefore, depression onset can be concluded to be a likely confounder in this analysis, and may account for the previously demonstrated association of WMHs and treatment outcomes in other studies, which did not assess the effect of this factor (Chen *et al*, 2006; Taylor *et al*, 2003; Teodorczuk *et al*, 2007). The significantly increased number of non-remitters in the early-onset LLD group may at first seem counterintuitive, provided the prevailing view that late-onset LLD is the more difficult to treat form of the disease. However, studies examining this association have been mixed, casting doubt on the validity of this perspective (Alexopoulos *et al*, 1996; Dew *et al*, 1997; Kozel *et al*, 2008; Reynolds *et al*, 1998). Overall, the findings of the exploratory analysis suggest that the intricate relationship between WMHs and remission status cannot fully be separated from other casual factors. Instead, it is likely more accurate to conceptualize WMHs as a manifestation of multiple underlying competing interactions, which ultimately affect LLD treatment outcomes.

Although this study is unable to fully elucidate etiological considerations, its results are able to demonstrate that WMH accumulation may be as important as cumulative WMH burden in the development and treatment trajectories of

Table 3 Exploratory Analysis

	Baseline	Follow-up	Mean difference (95% CI)	t-Score	d.f.	P-value
Antidepressant						
Escitalopram ($n=16$)	1.65×10^{-3} (2.61×10^{-3})	2.18×10^{-3} (2.84×10^{-3})	5.31×10^{-4} (6.27×10^{-5} to 9.98×10^{-4})	2.42	15	0.029*
Remitters ($n=8$)	1.02×10^{-3} (1.02×10^{-3})	1.37×10^{-3} (1.66×10^{-3})	3.48×10^{-4} (-4.45×10^{-4} to 1.14×10^{-3})	1.04	7	0.334
Non-remitters ($n=8$)	2.29×10^{-3} (3.56×10^{-3})	3.00×10^{-3} (3.60×10^{-3})	7.14×10^{-4} (2.60×10^{-5} to 1.40×10^{-3})	2.45	7	0.044*
Venlafaxine ($n=26$)	1.33×10^{-3} (1.51×10^{-3})	1.64×10^{-3} (2.23×10^{-3})	3.10×10^{-4} (-1.09×10^{-4} to 7.30×10^{-4})	1.52	25	0.140
Duloxetine ($n=5$)	7.62×10^{-4} (5.28×10^{-4})	5.28×10^{-4} (2.48×10^{-4})	-2.34×10^{-4} (-8.40×10^{-4} to 3.73×10^{-4})	−1.07	4	0.345
Depression onset						
Early onset ($n=32$)	1.10×10^{-3} (1.53×10^{-3})	1.48×10^{-3} (2.21×10^{-3})	3.80×10^{-4} (5.50×10^{-5} to 7.06×10^{-4})	2.39	31	0.023*
Remitters ($n=12$)	8.36×10^{-4} (5.01×10^{-4})	1.06×10^{-3} (6.68×10^{-4})	2.20×10^{-4} (-2.68×10^{-4} to 7.07×10^{-4})	0.99	11	0.343
Non-remitters ($n=20$)	1.26×10^{-3} (1.90×10^{-3})	1.73×10^{-3} (2.74×10^{-3})	4.77×10^{-4} (1.79×10^{-5} to 9.36×10^{-4})	2.18	19	0.042*
Late onset ($n=15$)	1.98×10^{-3} (2.44×10^{-3})	2.19×10^{-3} (2.67×10^{-3})	2.15×10^{-4} (-3.82×10^{-4} to 8.11×10^{-4})	0.77	14	0.453
Age (years)						
60–70 ($n=33$)	1.13×10^{-3} (1.60×10^{-3})	1.43×10^{-3} (2.26×10^{-3})	3.02×10^{-4} (-3.96×10^{-6} to 6.08×10^{-4})	2.01	32	0.053
>70 ($n=14$)	1.97×10^{-3} (2.40×10^{-3})	2.36×10^{-3} (2.55×10^{-3})	3.87×10^{-4} (-2.89×10^{-4} to 1.06×10^{-3})	1.24	13	0.238
CIRSG vascular						
Score: 0–1 ($n=9$)	5.72×10^{-4} (4.72×10^{-4})	9.27×10^{-4} (7.58×10^{-4})	3.55×10^{-4} (-5.75×10^{-5} to 7.68×10^{-4})	1.99	8	0.082
Score: 0–2 ($n=38$)	1.57×10^{-3} (2.04×10^{-3})	1.89×10^{-3} (2.57×10^{-3})	3.21×10^{-4} (-1.86×10^{-5} to 6.60×10^{-4})	1.92	37	0.063
Anti-inflammatory use						
None ($n=21$)	1.15×10^{-3} (2.11×10^{-3})	1.58×10^{-3} (2.24×10^{-3})	4.28×10^{-4} (8.72×10^{-5} to 7.70×10^{-4})	2.62	20	0.016*
Remitters ($n=7$)	7.08×10^{-4} (3.81×10^{-4})	1.12×10^{-3} (8.51×10^{-4})	4.15×10^{-4} (-2.97×10^{-4} to 1.13×10^{-3})	1.43	6	0.204
Non-remitters ($n=14$)	1.38×10^{-3} (2.58×10^{-3})	1.81×10^{-3} (2.69×10^{-3})	4.35×10^{-4} (-8.74×10^{-6} to 8.79×10^{-4})	2.12	13	0.054
>1 Agent ($n=26$)	1.56×10^{-3} (1.70×10^{-3})	1.81×10^{-3} (2.49×10^{-3})	2.46×10^{-4} (-1.98×10^{-4} to 6.89×10^{-4})	1.14	25	0.264
Benzodiazepine use						
None ($n=25$)	9.19×10^{-4} (1.08×10^{-3})	1.24×10^{-3} (1.39×10^{-3})	3.26×10^{-4} (-1.21×10^{-5} to 6.64×10^{-4})	1.99	24	0.058
>1 Agent ($n=22$)	1.90×10^{-3} (2.43×10^{-3})	2.23×10^{-3} (3.07×10^{-3})	3.29×10^{-4} (-1.61×10^{-4} to 8.19×10^{-4})	1.40	21	0.177

Abbreviations: CIRSG, Cumulative Illness Rating Scale-Geriatric; d.f., degrees of freedom.
Data are represented as mean (SD), unless otherwise indicated.

Table 4 Change in Gray Matter Volume, Hippocampal Volume, and Fractional Anisotropy

	Baseline	Follow-up	Mean difference (95% CI)	t-Score	d.f.	P-value
Remitters ($n=23$)						
nGMV (%)	3.20×10^{-1} (2.15×10^{-2})	3.20×10^{-1} (2.00×10^{-2})	1.06×10^{-4} (-4.16×10^{-3} to 4.37×10^{-3})	−0.05	22	0.96
nHCV (%)	5.86×10^{-3} (5.07×10^{-4})	5.98×10^{-3} (4.32×10^{-4})	1.20×10^{-4} (-9.07×10^{-6} to 2.49×10^{-4})	−1.93	22	0.07
FA	3.74×10^{-1} (1.22×10^{-2})	3.73×10^{-1} (1.44×10^{-2})	-9.11×10^{-4} (-3.86×10^{-3} to 2.04×10^{-3})	0.64	22	0.53
Non-remitters ($n=24$)						
nGMV (%)	3.20×10^{-1} (2.04×10^{-2})	3.17×10^{-1} (2.19×10^{-2})	-3.39×10^{-3} (-8.38×10^{-3} to 1.61×10^{-3})	1.40	23	0.17
nHCV (%)	5.83×10^{-3} (6.29×10^{-4})	5.72×10^{-3} (5.68×10^{-4})	-1.08×10^{-4} (-2.59×10^{-4} to 4.18×10^{-5})	1.49	23	0.15
FA	3.72×10^{-1} (1.34×10^{-2})	3.72×10^{-1} (1.18×10^{-2})	-8.86×10^{-4} (-4.54×10^{-3} to 2.76×10^{-3})	0.50	23	0.62

Abbreviations: d.f., degrees of freedom; FA, fractional anisotropy; nGMV, normalized gray matter volume; nHCV, normalized bilateral hippocampus volume.
Data are represented as mean (SD), unless otherwise indicated.

LLD. The vascular depression hypothesis has been supported by numerous studies showing that development of late-onset LLD is associated with greater severity of WMHs. Furthermore, research has demonstrated that baseline WMHs are associated with treatment outcomes in these patients (Heiden *et al*, 2005; O'Brien *et al*, 1998). Our results were able to demonstrate that non-remitters had higher baseline WMHs compared with responders, but this difference was nonsignificant. The more robust association was found between accumulation of WMHs over 12 weeks and failure

to enter remission during this interval. These findings are corroborated by the work of Taylor *et al* (2003) who were the first group to demonstrate the importance of WMH accumulation in the treatment of LLD. They followed a cohort of 133 depressed elderly patients over 2 years, and observed significantly more WMH accumulation in those patients who were unable to achieve sustained remission with standard pharmacotherapy. Other groups have been able to replicate these findings over similarly long time spans (Chen *et al*, 2006; Teodorczuk *et al*, 2007). The novelty of the current study is its demonstration of comparable findings over the much shorter interval of 12 weeks. Extrapolating this study's mean change in non-nWMHs out to 2 years ($0.96\,cm^3$) yields results of comparable magnitude to calculated 2-year differences from Taylor *et al.* (2003) ($1.53\,cm^3$) and Chen *et al.* (2006) ($1.67\,cm^3$). The discrepancy in these values may suggest an acceleration of WMH accumulation overtime among LLD patients, but given the differences in study design this interpretation is merely speculative.

In this study's secondary analysis, a marginally nonsignificant increase in bilateral hippocampal volumes ($P=0.07$) was demonstrated in treatment responders. Reduction in hippocampal volumes in patients with depression has been extensively documented in the literature (Campbell *et al*, 2004; Videbech and Ravnkilde, 2004). The duration of depression has also been shown to be inversely correlated with hippocampal volume, which has prompted many to hypothesize that depression mediates hippocampus neurotoxicity (MacQueen *et al*, 2003; Sheline *et al*, 1996). Research into antidepressant therapy's effect on hippocampal volume is still very limited. Animal models have been able to demonstrate that chronic antidepressant administration, including SSRI and SNRI agents, mediates neurogenesis and increased hippocampal volumes (Hajszan *et al*, 2005; Malberg *et al*, 2000). In patients with posttraumatic stress disorder, Vermetten *et al* (2003) demonstrated that paroxetine administration over a treatment period of 9–12 months was associated with an increase in mean hippocampal volume and reduction of symptoms. However, the evidence for a similar effect in depression is currently non-existent, with the only published study by Vythilingam *et al* (2004) not finding any difference in hippocampal volume in 22 depressed patients over 7 months of treatment with an SSRI. The results of the present study may suggest that antidepressant-stimulated hippocampal neurogenesis is indeed occurring during treatment of depression, but that the effect is differentially distributed based on treatment response. Measureable differences in hippocampal volume may also take considerably longer than 12 weeks to develop despite the presence of neurogenesis. Unfortunately, the nonsignificant nature of this finding and the study's methodological limitations preclude any real conclusions from being drawn. Rather, this finding simply stands to highlight this as an area that may yield more substantive results with further research.

This study's primary limitation was its inclusion of patients from multiple clinical trials. This resulted in patients undergoing distinct treatment protocols and being assessed with different sets of depression rating scales (HRSD, MADRS). Although care was taken to select similar remission thresholds between these two scales, it is possible that variations in these instruments resulted in non-uniform remission classifications that impacted the results. The absence of a control group in this analysis is also an important limitation to recognize as it makes it difficult to assess the presence of any systematic measurement bias. Additionally, individual patient physiological factors, which were not assessed, may have influenced this study's findings. Most notably, patient hydration status has been shown to affect brain volumes, but the specific effect on hippocampal volumes and WMH burden has not yet been demonstrated and requires further study (Streitburger *et al*, 2012). It is important to note that this study did not have exclusion criteria based on prior antidepressant treatment nor require a minimum antidepressant free interval before beginning the study. Therefore, previous antidepressant treatment, especially proximal to the study, may have impacted the various markers we investigated. Finally, it is essential to realize that accumulation of WMHs is likely related to multiple factors, and this investigation's limited sample size prevent it from being able to fully explicate these details.

This study contributes to growing evidence that WMHs are associated with LLD. Our findings expand upon existing knowledge by demonstrating that WMH accumulation occurs over significantly shorter intervals (ie 12 weeks) than has been previously shown. Additionally, these changes are differentially distributed among those patients who are eventually classified as non-remitters, which indicates that the relationship between WMH accumulation and LLD is consequential even during short antidepressant treatment courses.

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