Quantitative analysis of MR-defined white matter hyperintensities in late-life depression.

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Introduction: Patients with late-life depression (LLD) have been shown to have more MRI-defined white matter hyperintensities (WMHs) than controls or patients with early-onset depression[1,2]; these lesions may result from vascular/ischemic damage and may contribute to LLD by disconnecting brain regions involved in mood regulation. Better characterizing the volume and location of WMHs in LLD patients will improve our understanding of the pathophysiology of LLD. In this study, we used a Gaussian fitting method and a semi-automated, segmentation approach to calculate WMH volume in LLD patients and controls. We hypothesized that LLD patients would have a greater WMH volume compared to controls and that WMH differences would be greater in brain regions associated with mood regulation.

Methods: A. Subject: All subjects were 60 years or older, non-demented and generally healthy or with stable medical conditions. LLD patients had (1) first depressive episode after 50 years of age and (2) no bipolar disorder, psychosis or other significant psychiatric comorbidity. Controls (CON) had no history of depression or other significant psychiatric disorder. Subjects remained on medications for the MRI scan with dose(s) stable for at least two weeks. **B. Image Acquisition:** All subjects were imaged with a 3.0-T Siemens scanner for T1-weighted 3-D structural and Fluid Attenuation Inversion Recovery (FLAIR) imaging. **C. Image Processing: 1. RF In-homogeneity Correction:** To correct the RF in-homogeneity, a simple and rapid correction algorithm was applied to FLAIR data[3]. **2. Co-register / Normalization / Segmentation:** These three steps were performed by SPM 5. The procedures include (1) co-registration of FLAIR(Source) and T1(Reference) on same subject, (2) spatial normalization of T1 into Talairach space, (3) spatial normalization of co-registered FLAIR by parameters that was created by T1 spatial normalization, and (4) segmentation of T1 images based on ICBM 452 Atlas probability map. **3. Extraction of White Matter:** To extract white matter regions, FLAIR images were masked with the segmentation of the T1 images. **4. Determination of Threshold value:** A mixture of 3 Gaussian curves was fit to the histogram of FLAIR white matter images (Figure 1). The threshold value was determined by the crossing point between the third Gaussian fitting curve and histogram. **5. Definition of VOIs:** Ten VOIs (left and right for five regions) were defined from T1-weighted 3-D structural MR images. They were: orbitofrontal (OF), prefrontal (PF), dorsolateral frontal (DLF); parietal (Par); and occipitotemporal (OT)[4]. **6. Detection of WMHs:** WMH areas were identified as pixels FLAIR white matter images that are above the threshold and the WMH volume was measured in each VOI. **D. Statistical Analysis:** Statistical analyses were performed using SPSS 13.0. Demographic and baseline characteristics of the two groups (LLD and CON) were compared. ANOVA was used to assess for WMH volume differences between the two groups, controlling for any baseline differences. Comparisons were made for total brain WMH volume and for WMH volume within each VOI. A p value of 0.05 (uncorrected for multiple comparisons) was selected as the level of significance.

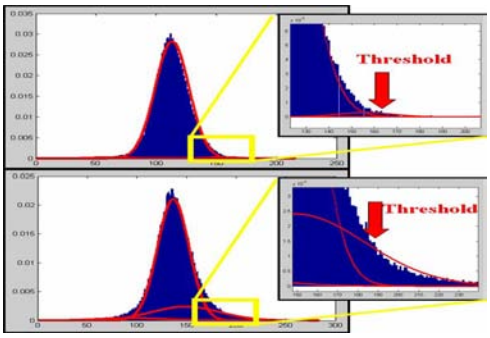

Figure 1. A mixture of three Gaussian fitting for determining Threshold; Control (Top) and LLD patient (Bottom)

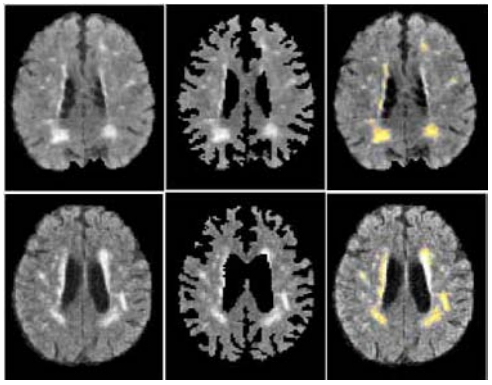

Figure 2. Two LLD patients FLAIR image (Left), Segmented WM image (Center), Detected WMHs (Right)

Results: Thirteen subjects (4 LLD, 9 CON) showed no significant differences in age, gender, race/ethnicity or potential risk factors for WMHs (history of hypertension, diabetes, smoking status); however, there was a difference in mean arterial pressure (MAP) between the groups (Table 1). MAP was therefore used as a covariate in subsequent analyses. Areas of WMH in two representative LLD patients are shown in Figure 2. Differences in WMH volume between the groups are shown in Figure 3.

Table 1. Demographic and clinical characteristics

Variable	Group		Statistic
	LLD(N=4)	CON(N=9)	
Age (mean [SD])	71.0[9.8]	68.0[6.5]	t=-0.66, df=11, p=0.522
Gender (female/male)	2/2	4/5	Fisher's p=1.000
Race/Ethnicity (Caucasian/non-Caucasian)	3/1	7/2	Fisher's p=1.000
Hypertension (yes/no)	3/1	7/2	Fisher's p=1.000
Diabetes (yes/no)	1/3	1/8	Fisher's p=1.000
Smoker (yes/no)	1/3	2/7	Fisher's p=1.000
MAP (mean [SD])	107.6 [11.6]	94.2 [7.7]	t=-2.31, df=10, p=0.043*
MMSE (mean [SD])	28.0 [1.4]	29.2 [1.1]	t=1.71 , df=11, p=0.115
HAMD (mean [SD])	26.0 [5.4]	3.0 [2.4]	t=-10.97, df=11, p<0.001*
BDI (mean [SD])	29.5 [1.0]	4.9 [4.2]	t=-16.46, df=11, p<0.001*

MAP=mean arterial pressure; MMSE=Mini-Mental Status Examination; HAMD=24-itme Hamilton Depression Rating Scale; BDI=Beck Depression Inventory; *p<0.05.

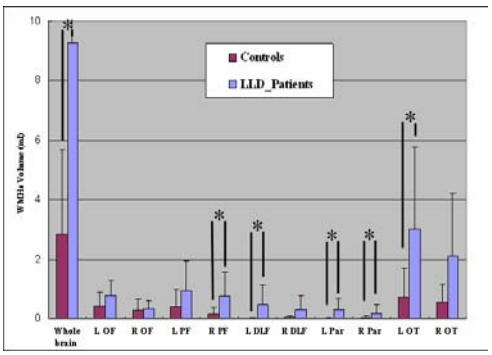

Figure 3. Differences in WMH volum (LLD vs. Con) *p<0.05.

Discussion: As hypothesized, LLD patients were found to have a greater total WMH volume compared to controls. Additionally, LLD patients showed greater regional WMH volume in right prefrontal, left dorsolateral frontal, left and right parietal and left occipitotemporal. Prefrontal, dorsolateral frontal and parietal brain regions have been clearly implicated in the pathophysiology of depression[5]; occiptotemporal regions have been less frequently implicated, and their role in depression should be evaluated further. Limitations of this study include small sample size and lack of control for multiple comparisons. Despite these limitations, these preliminary results support the use of this segmentation method for the quantification of WMH.

References: [1] Wen W, et al., *NeuroImage* 2004, 22:144-145. [2] Greenwald BS, et al., *Stroke* 1998, 29(3):613-617. [3] Cohen MS, et al., *Human Brain Mapping* 2000, 10:204-211. [4] Tullberg M, et al., *Neurology* 2004, 63:246-253. [5] Mayberg HS, *Br Med Bull* 2003, 65:193-207.