Integration of Neuroimaging in the Assessment of Late Life Depression

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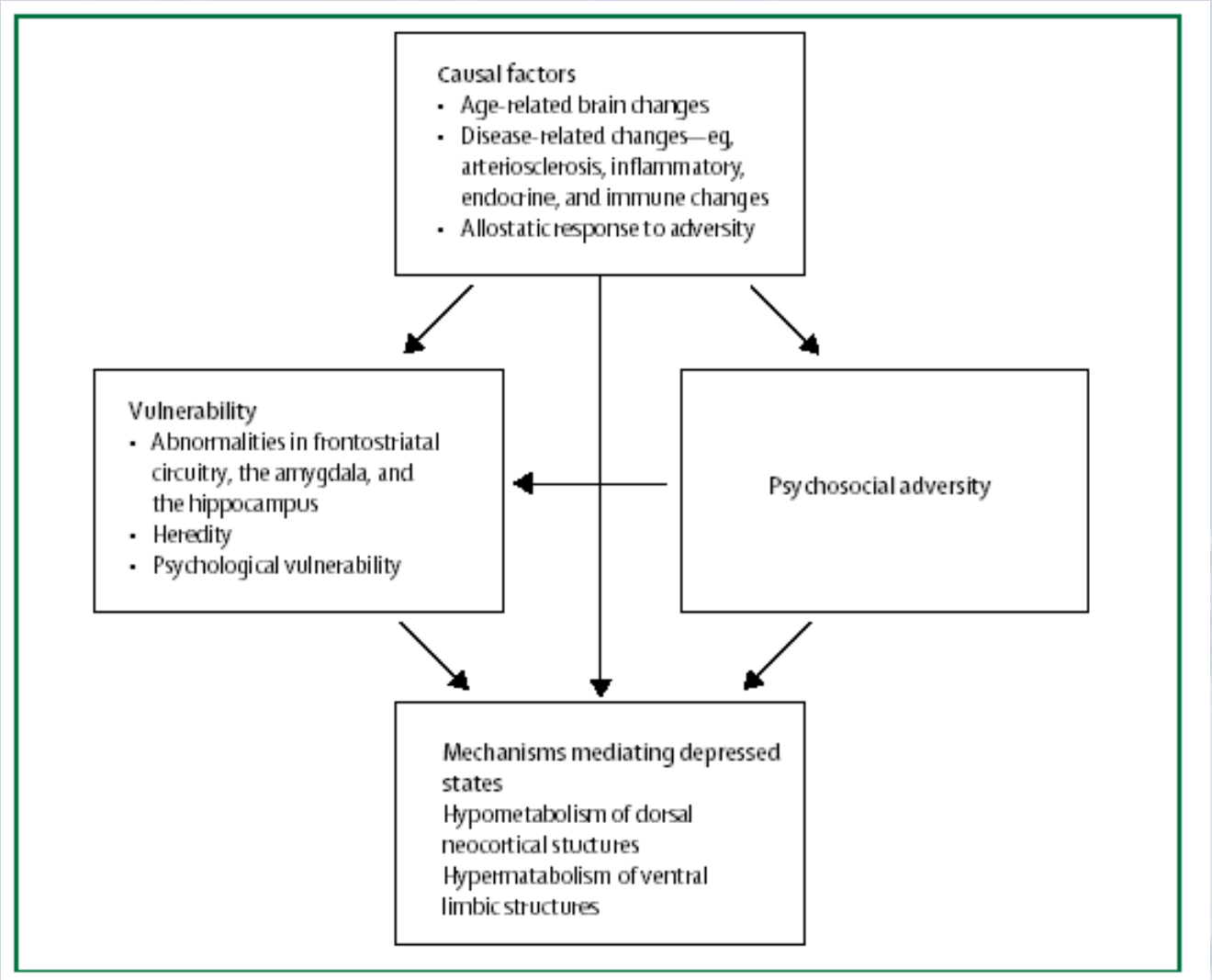
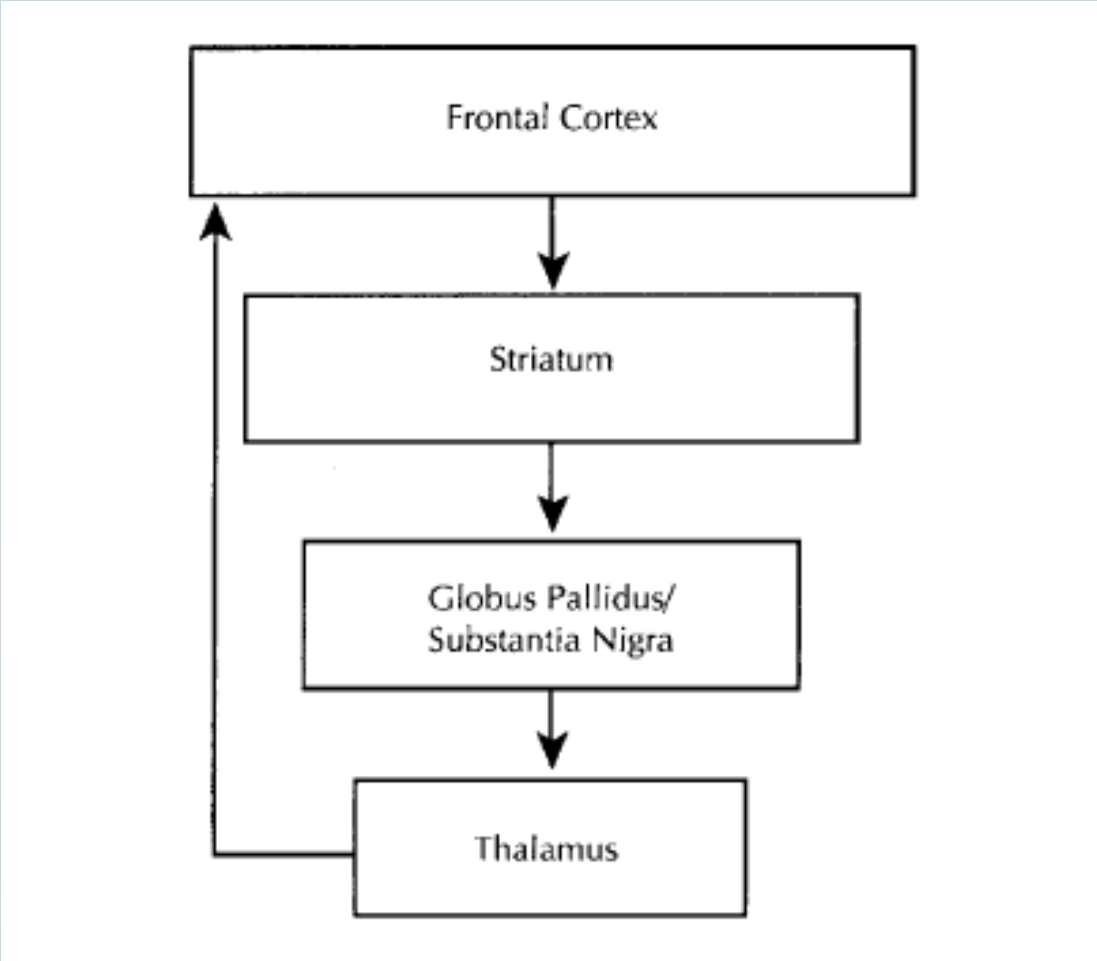
Model of Late-Life Depression with Brain dysfunction

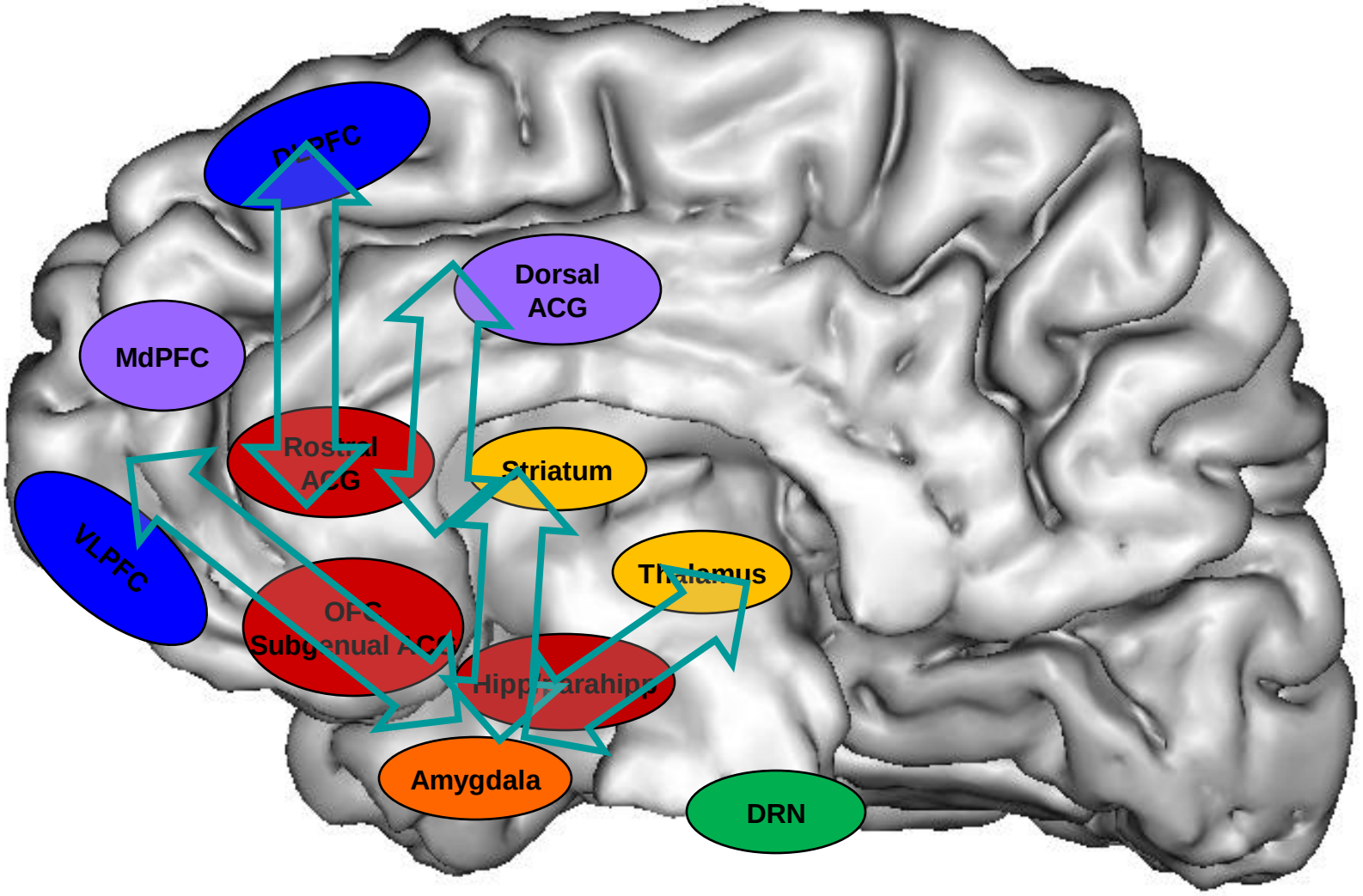


(Alexopoulos GS. *Lancet* 2005;365:1961-70)

General structure of frontal subcortical circuits



Limbic-Cortical Dysregulation: Model of Depression



Neuroimaging Concepts

- **Structural Imaging**
  - MRI (White Matter Lesions)
  - Diffusion Tensor Imaging
  - MR Spectroscopy
- **Functional Imaging**
  - SPECT
  - PET
  - fMRI

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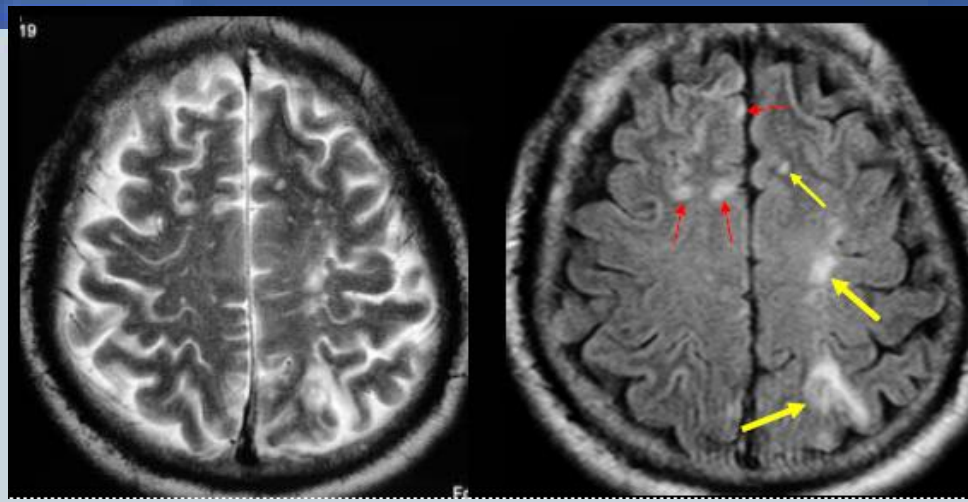
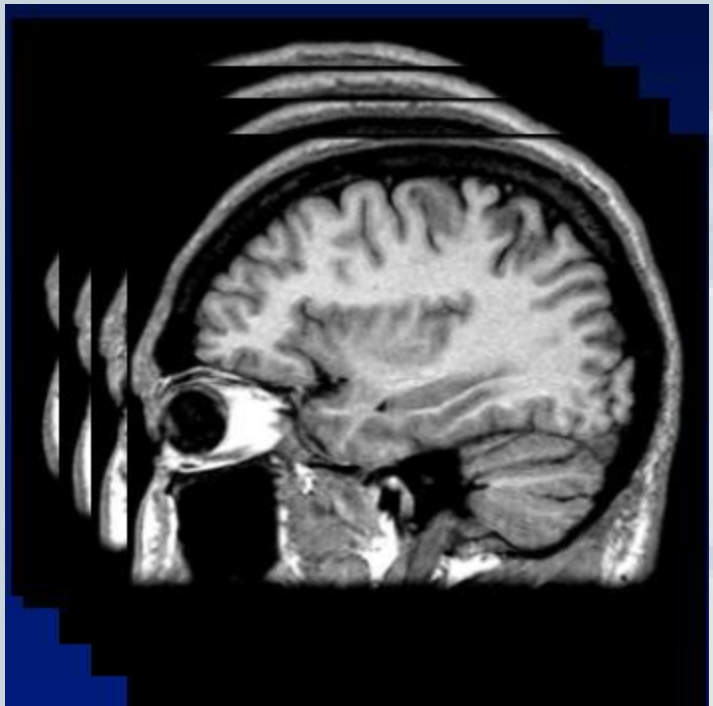
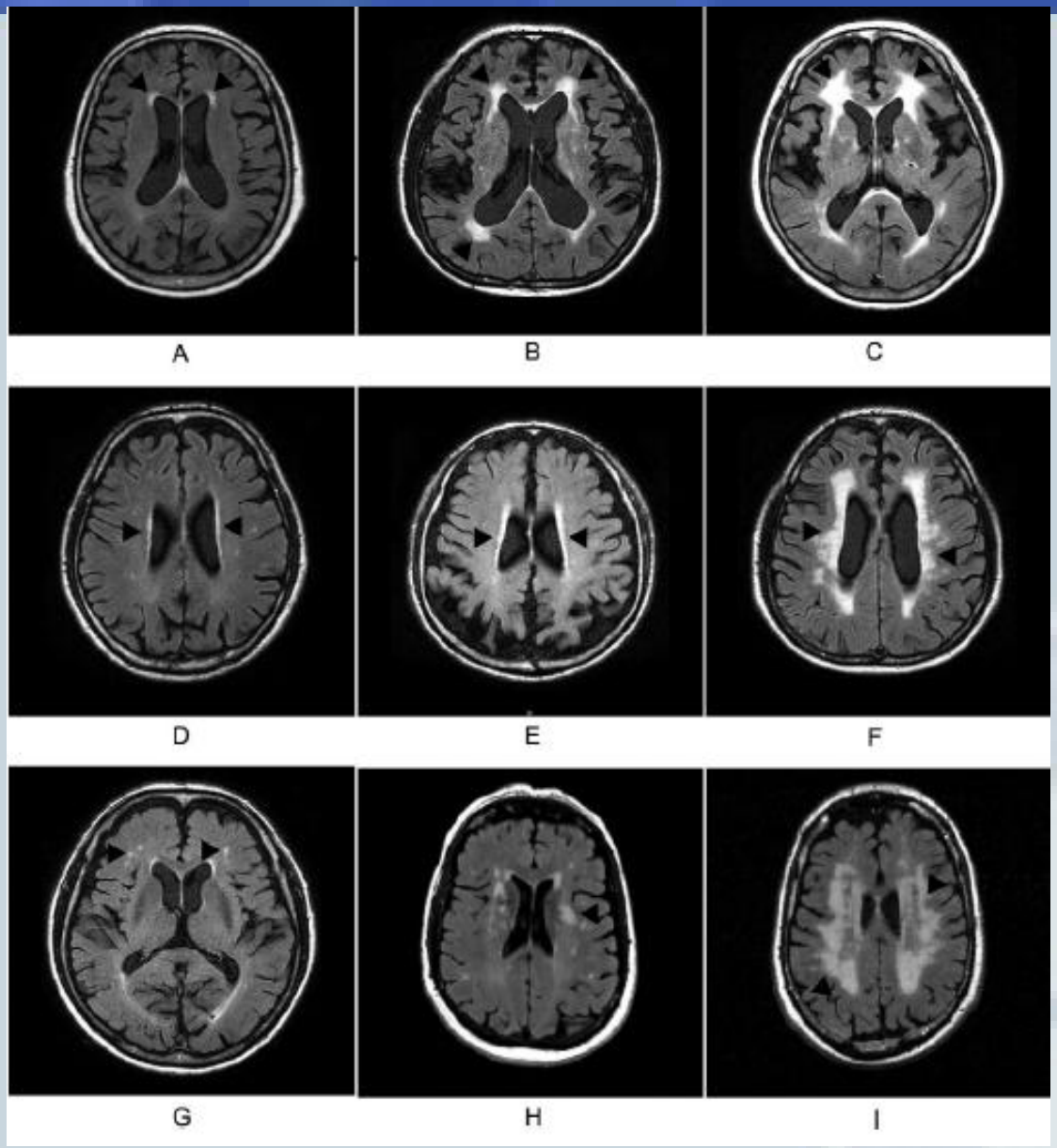




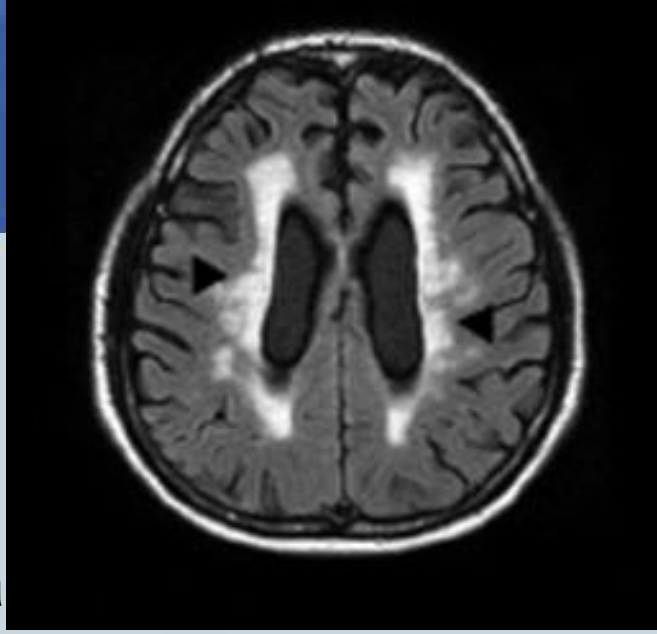
White Matter Lesions (WMLs)



Vascular burden on Late-Life Depression

- **Chronic ischemic damage is an important cause of depression**
  - Silent cerebral infarction (Fujikawa et al, 1993)
  - Arteriosclerotic depression (Krishnan and McDonald, 1995)
  - Cerebrovascualar disease may contribute to the development of a late-onset depression syndrome (Krishnan and McDonald, 1995)
- **Vascular depression hypothesis**
  - High rate of depression in patients with hypertension, diabetes, and coronary disease
  - High rate of depression in stroke patients
  - Frequent occurrence of silent stroke and white matter hyperintensities in late-onset depression
  - Infrequent family history of depression occuring in the context of silent stroke

Functional Correlates



- **PVWMLs**
  - Risk of dementia
  - Severity of cognitive impairment in dementia
  - Psychomotor speed in nondemented elderly
  - Rate of cognitive decline
  - Medial temporal lobe atrophy
- **DWMLs**
  - Risk and outcomes of depression
  - Severity of cognitive impairment in depression
- **SCG (Subcortical gray matter) Lesions**

Histopathologic Correlates

- **Periventricular caps and smooth halo**
  - Demyelination associated with Ependymal loss and subependymal gliosis
  - Venous congestion due to noninflammatiory periventricular venous collagenosis
  - Nonischemic in nature /Wallerian degeneration
- **Irregular PVWMH and DWMH**
  - Microcystic infarct
  - Patchy rarefaction of myelin
  - Ischemic in nature/ not Wallerian degeneration

WMLs and LLD

Anatomic location and laterality of MRI signal hyperintensities in late-life depression

Larry A. Tupler[a,*], K. Ranga R. Krishnan[a], William M. McDonald[b], Carrie B. Dombeck[a], Sean D'Souza[a], David C. Steffens[a]

Modified Fazekas ratings and *P* values for analyses comparing elderly depressed patients ($n=115$), late-onset depressives ($n=69$), early-onset depressives ($n=46$), and elderly controls ($n=37$)

Region	Rating 0	1	2	3	Patients vs. controls *P* value[a]	LOD vs. controls *P* value[b]	EOD vs. controls *P* value[b]	LOD vs. EOD *P* value[b]
PVH					.071	.018	.127	.002
Patients	2	49	30	34				
LOD patients	0	18	24	27				
EOD patients	2	31	6	7				
Controls	0	20	13	4				
DWMH-F					.02	.008	.057	.01
Patients	34	16	32	33				
LOD patients	10	10	23	26				
EOD patients	24	6	9	7				
Controls	11	9	15	2				
SCG-F					.001	.001	.01	.123
Patients	59	9	17	30				
LOD patients	29	5	11	24				
EOD patients	30	4	6	6				
Controls	30	4	3	0				

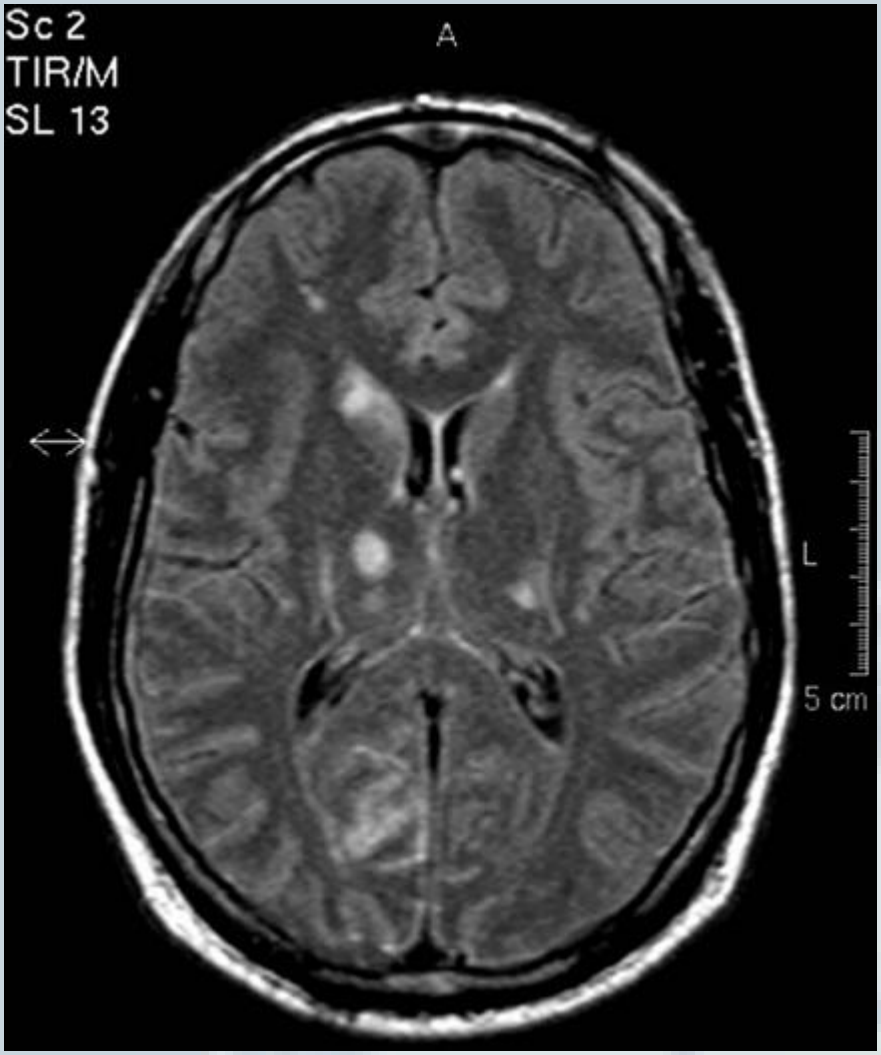
(Tupler, J psychosom research, 2002)

DWMLs and LLD

- **Onset of Depression**
  - First onset of depression over age 50 (Simpson, 2000)
  - More severe lesions in DWMLs associated with late-onset depression (Tupler, 2002)
- **Outcomes of Depression**
  - Poor response to treatment (Steffens, 1998)
  - Increased mortality in depression older patients (Levy, 2003)
  - High HAMD score, severe longitudinal courses, lower MMSE (Heiden, 2005)
  - Higher relapse rate of depression (Taylor, 2003)

SCGs and LLD

- **Greater severity and volume**
  - Psychomotor slowing in LLD
  - Poorer Executive dysfunction
- **Early vs LLD ?**
  - Considering Age, CVRFs
  - No difference



Location of WML and LLD

Lobar Distribution of Lesion Volumes in Late-Life Depression: The Biomedical Informatics Research Network (BIRN)

James R MacFall*[,1], Warren D Taylor[2], David E Rex[3], Steve Pieper[4], Martha E Payne[2], Douglas R McQuoid[2], David C Steffens[2], Ron Kikinis[4], Arthur W Toga[3] and K Ranga Rama Krishnan[2]

Table 1 Initial White Matter Lesion Volume by Lobe: Association with Depression Status

	Depressed (SE)	Control (SE)	Mean difference	Parameter estimate	t-value	p-value
Total brain WMH lesion volume	6.11 (0.90)	3.09 (1.02)	3.02	1.36	2.23	0.0283
Left hemisphere WMH lesion volume	2.95 (0.41)	1.63 (0.47)	1.32	0.62	2.12	0.0363
Right hemisphere WMH lesion volume	3.16 (0.50)	1.46 (0.56)	1.70	0.75	2.27	0.0254
Total frontal lobe WMH lesion volume	4.17 (0.46)	2.37 (0.52)	1.80	0.69	2.63	0.0101
Left frontal lobe WMH lesion volume	2.02 (0.21)	1.22 (0.24)	0.80	0.31	2.55	0.0123
Right frontal lobe WMH lesion volume	2.16 (0.26)	1.15 (0.29)	1.01	0.39	2.56	0.0120
Total parietal lobe WMH lesion volume	1.87 (0.46)	0.74 (0.45)	1.13	0.70	1.62	0.1084
Left parietal lobe WMH lesion volume	0.91 (0.21)	0.43 (0.21)	0.48	0.33	1.47	0.1451
Right parietal lobe WMH lesion volume	0.96 (0.25)	0.31 (0.28)	0.65	0.37	1.76	0.0814

(MacFall,, Neuropsychopharmacology, 2006)

Location of WML and LLD

Regional White Matter Hyperintensity Burden in Automated Segmentation Distinguishes Late-Life Depressed Subjects From Comparison Subjects Matched for Vascular Risk Factors

Yvette I. Sheline, M.D.

Joseph L. Price, Ph.D.

S. Neil Vaishnavi, B.S.

Mark A. Mintun, M.D.

Deanna M. Barch, Ph.D.

Adrian A. Epstein, B.A.

Consuelo H. Wilkins, M.D.

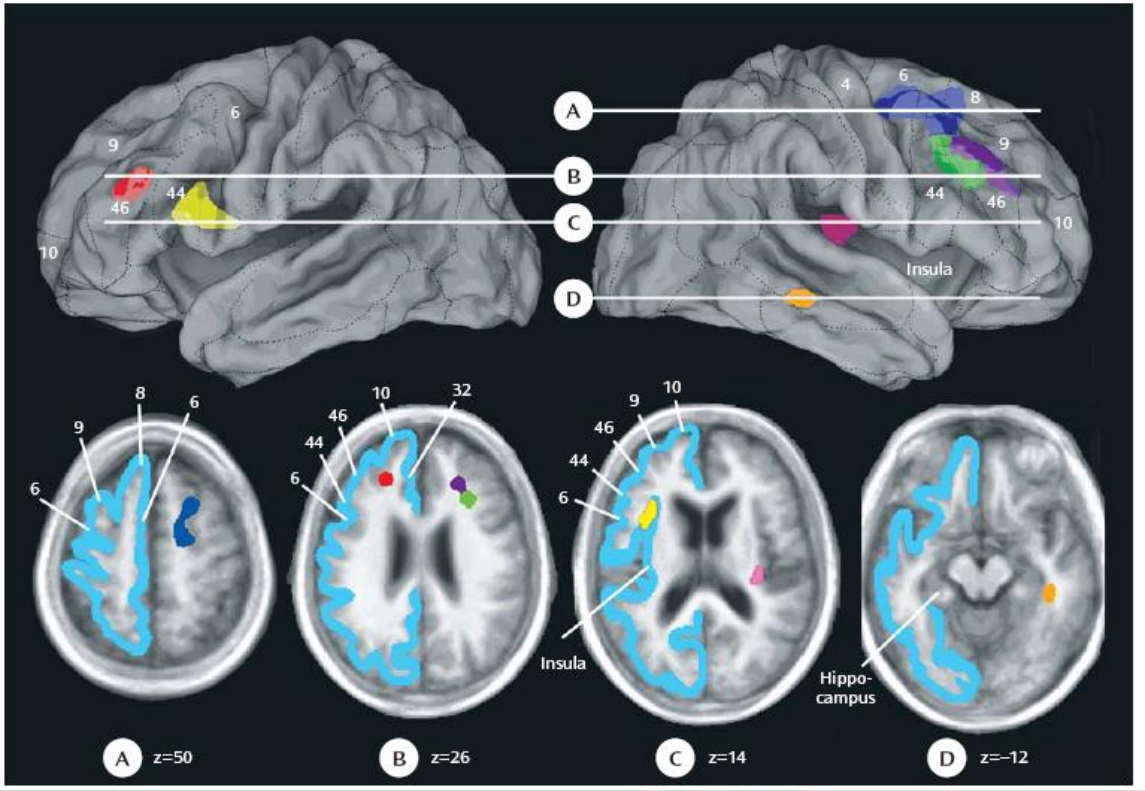
Abraham Z. Snyder, M.D.

Lars Couture, B.A.

Kenneth Schechtman, Ph.D.

Robert C. McKinstry, M.D., Ph.D.

FIGURE 2. Differences Between Depressed Patients and Comparison Subjects in Regional White Matter Hyperintensity Volumes[a]



(Sheiline, Am J Psychiatry, 2008)

Orbitofrontal Cortex, SCG and LLD

Subcortical Lesion Severity and Orbitofrontal Cortex Volume in Geriatric Depression

Shwu-Hua Lee, Martha E. Payne, David C. Steffens, Douglas R. McQuoid, Te-Jen Lai, James M. Provenzale, and K. Ranga Rama Krishnan

Table 1. Demographic, Clinical, and Neuroimaging Characteristics of the Sample

	Patient *n*	Control *n*	*p*
Gender			
Female, *n* (%)	21 (51.22)	34 (82.93)	.0023
Male, *n* (%)	20 (48.78)	7 (17.07)	
Age, Years, Mean (SD)	68.73 (6.98)	71.15 (6.25)	.1029
Education, Years, Mean (SD)	13.244 (3.390)	15.146 (1.944)	.0027
Mini Mental State Examination Score, Mean (SD)	28.171 (2.010)	29.050 (1.037)	.0195
Cumulative Illness Rating Scale Score, Mean (SD)	3.927 (3.028)	2.732 (2.540)	.0564
Right Orbital Frontal Cortex Volume, mL, Mean (SD)	6.44 (1.74)	7.12 (1.37)	.0532
Total Orbital Frontal Cortex Volume, mL, Mean (SD)	12.11 (2.09)	14.06 (2.53)	.0114
Total Brain Volume, mL, Mean (SD)	1352.16 (184.55)	1299.10 (130.91)	.1376
Left Orbital Frontal Cortex/Total Brain, Mean (SD)	.0045 (.0009)	.0051 (.0011)	.0078
Right Orbital Frontal Cortex/Total Brain, Mean (SD)	.0047 (.0009)	.0055 (.0011)	.0010
Total Orbital Frontal Cortex/Total Brain, Mean (SD)	.0092 (.0016)	.0106 (.0020)	.0008

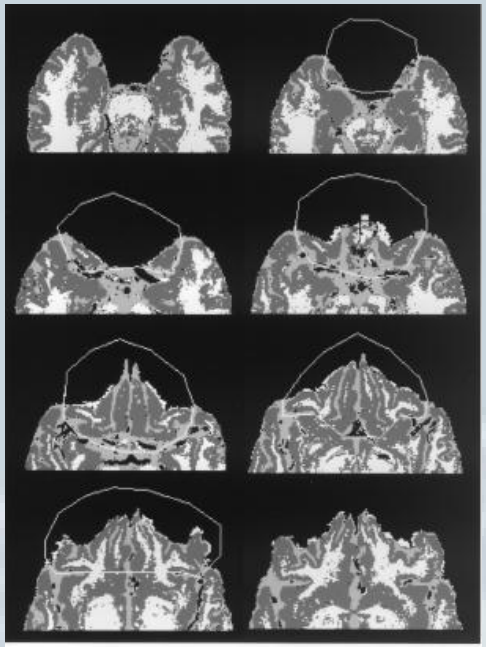


Figure 1. Tracing of orbitofrontal gyri on segmented scan (from inferior to superior).

(Lee, Biol Psychiatry, 2003)

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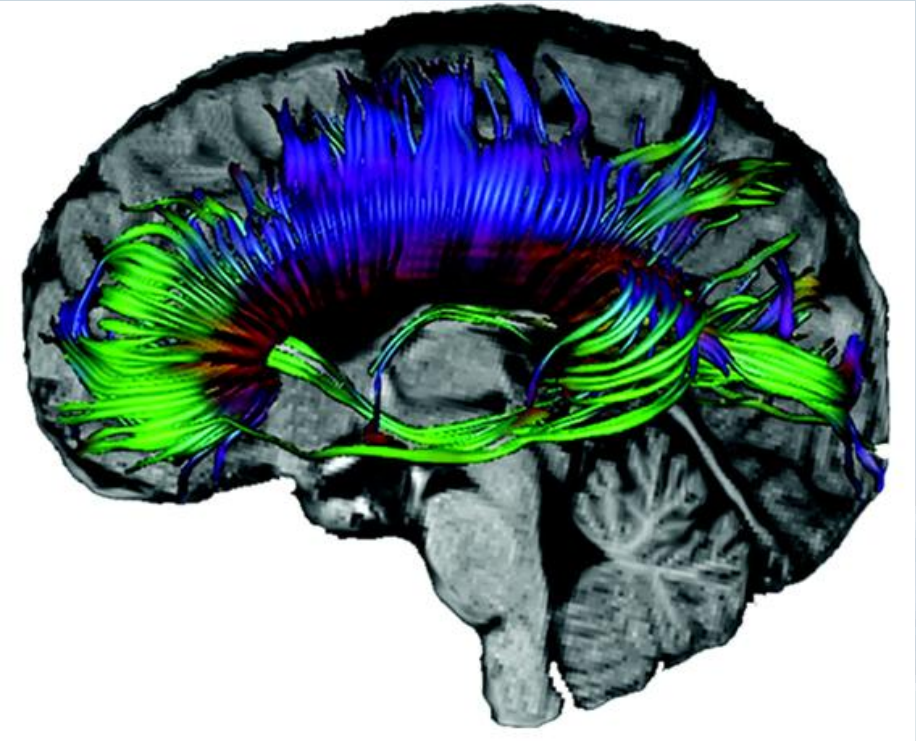


Anisotropy

Marker of tissue structural integrity

Microstructural Abnormality of WM in LLD

Dorsolateral Prefrontal Cortex and Anterior Cingulate Cortex White Matter Alterations in Late-Life Depression

Jae Nam Bae, James R. MacFall, K. Ranga R. Krishnan, Martha E. Payne, David C. Steffens, and Warren D. Taylor

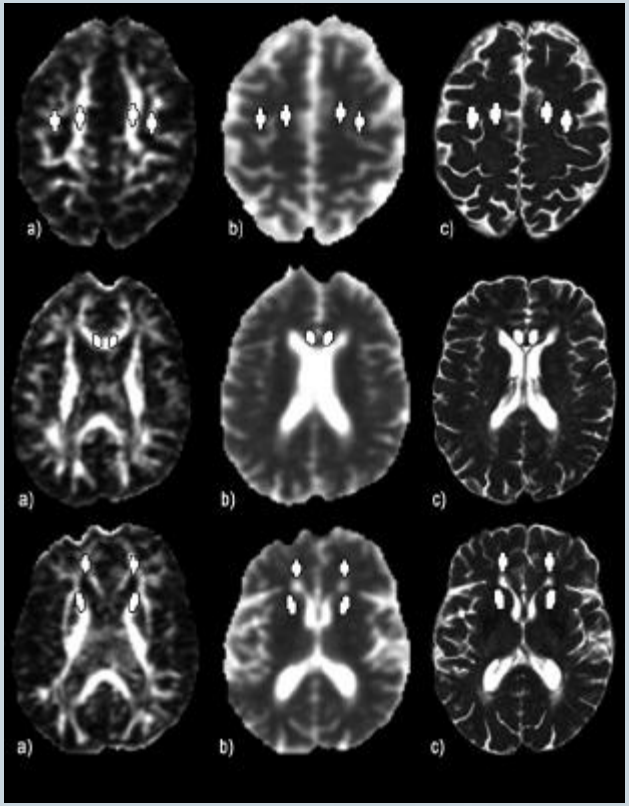


Table 2. Adjusted Differences Between Groups for DTI Measures

	ADC Values		FA Values	
	F Value	*p* Value	*F* Value	*p* Value
Corpus Callosum	3.04	.0827	1.51	.2203
Left Internal Capsule	3.43	.0655	.40	.5261
Right Internal Capsule	.93	.3352	2.04	.1546
Left ACC	.37	.5442	.40	.5254
Right ACC	1.73	.1898	3.90	.0498
Left Superior Frontal Gyrus	.46	.5005	5.73	.0176
Right Superior Frontal Gyrus	.00	.9972	4.32	.0391
Left Middle Frontal Gyrus	1.21	.2731	8.97	.0031
Right Middle Frontal Gyrus	.47	.4945	3.81	.0525

(Bae, Biol Psychiatry, 2006)

Microstructural Abnormality of WM in LLD

Diffuse Microstructural Abnormalities of Normal-Appearing White Matter in Late Life Depression: A Diffusion Tensor Imaging Study

Joshua S. Shimony, Yvette I. Sheline, Gina D'Angelo, Adrian A. Epstein, Tammie L.S. Benzinger, Mark A. Mintun, Robert C. McKinstry, and Abraham Z. Snyder

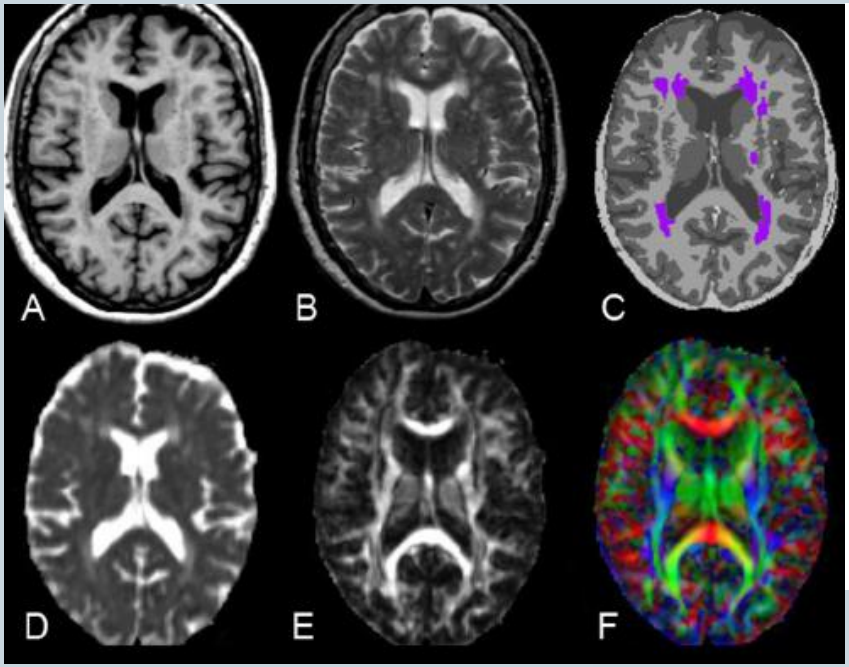


Table 2. Summary Statistics for Deep WM and Superficial WM (RA and MD)

	Depressed		Control Subjects		
	n	Mean (SD)	*n*	Mean (SD)	p^a
Deep WM RA	75	.27 (.025)	23	.28 (.019)	.6931
Deep WM MD	75	.76 (.043)	23	.74 (.037)	.0014
CC RA	73	.63 (.068)	23	.66 (.0557)	.0640
CC MD	73	.79 (.090)	23	.75 (.074)	.0062
Prefrontal WM RA	78	.32 (.027)	22	.34 (.027)	.0043
Prefrontal WM MD	78	.76 (.044)	22	.73 (.036)	.0004
Non-Prefrontal WM RA[b]	77	.35 (.031)	22	.36 (.026)	.4314
Non-Prefrontal WM MD[b]	77	.80 (.037)	22	.77 (.033)	<.0001

(Shimony, Biol Psychiatry 2009)

Microstructural Abnormality of WM in LLD

Microstructural White Matter Abnormalities and Remission of Geriatric Depression

(Alexopolus, Am J Psychiatry, 2008)

George S. Alexo

Christopher F. M

Faith M. Gunni

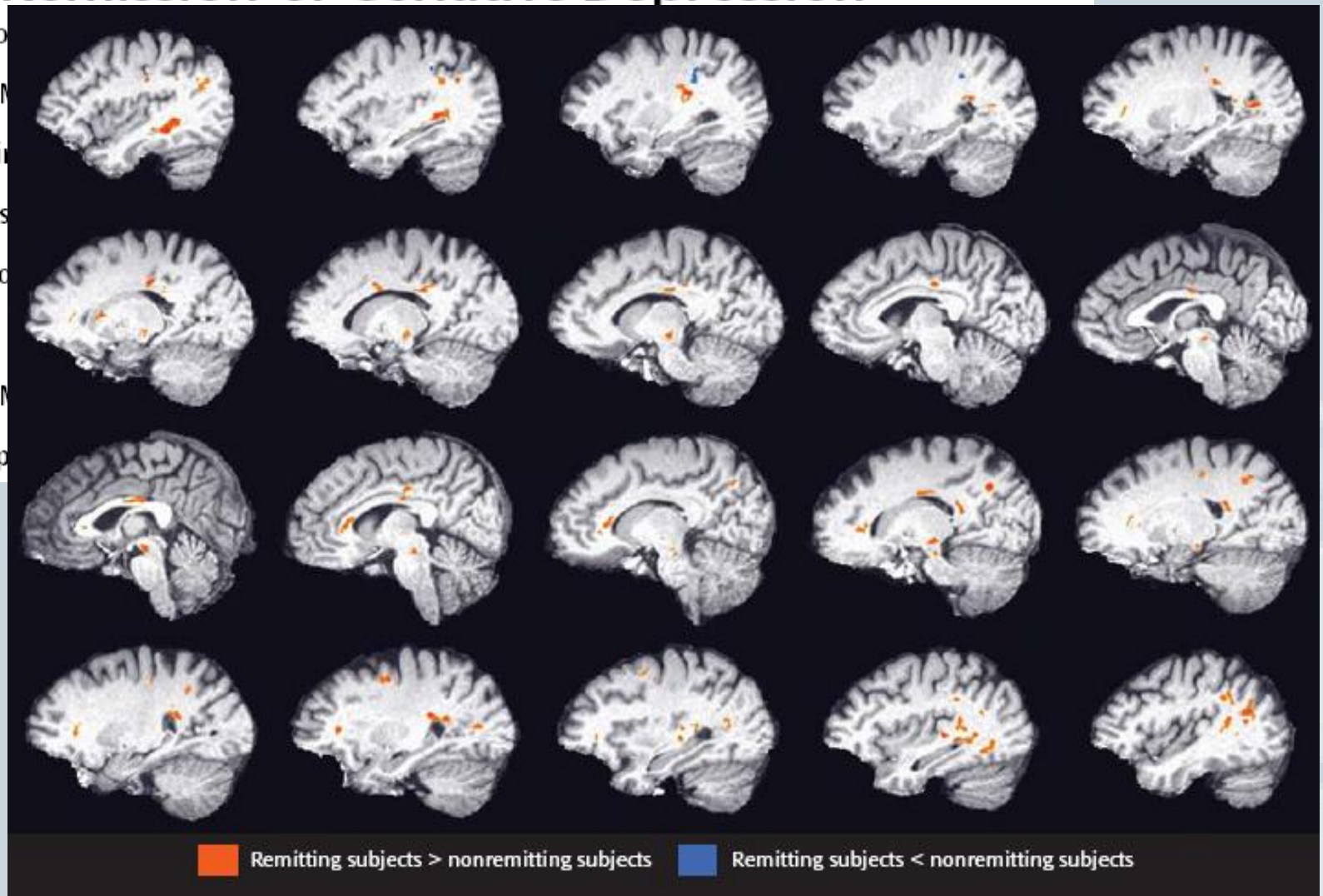
Vassilios Latous

Dora Kanellopo

Sibel Klimstra,

Kelvin O. Lim, M

Matthew J. Hop



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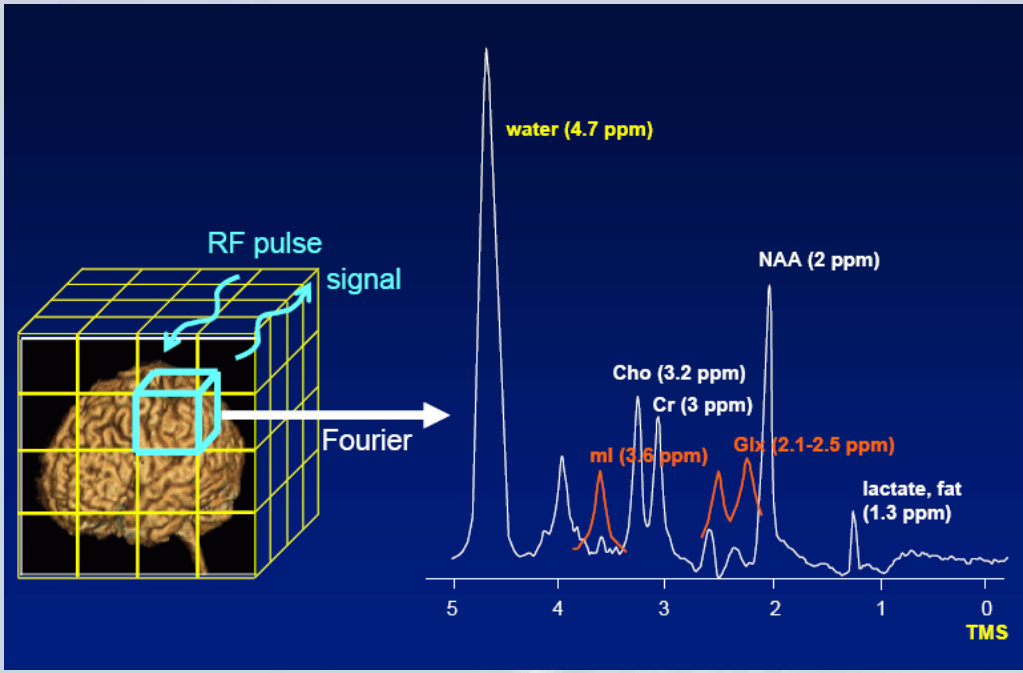


- NAA : neuronal integrity 반영, 대부분의 질환에서 감소
- Cho : cell membrane integrity, synthesis와 관련
  종양, gliosis, membrane disruption에서 증가
- Cr : internal reference (모든 질환에서 별 변화 없음)
- Lactate : hypoxia, ischemia에서 증가
  허혈성 뇌졸중과 악성 종양에서 증가
- Myo-inositol : Alzheimer에서 증가

Abnormal Brain Metabolite Level in LLD

MRI white matter hyperintensities, ^{1}H-MR spectroscopy and cognitive function in geriatric depression: a comparison of early- and late-onset cases

Tetsuhito Murata[1]*, Hirohiko Kimura[2], Masao Omori[1], Hirotsugu Kado[2], Hirotaka Kosaka[1], Tetsuya Iidaka[3], Harumi Itoh[2] and Yuji Wada[1]

Table 1. Subject characteristics, MRI/^{1}H-MRS and neuropsychological findings in elderly depressed patients: comparison of early-onset and late-onset

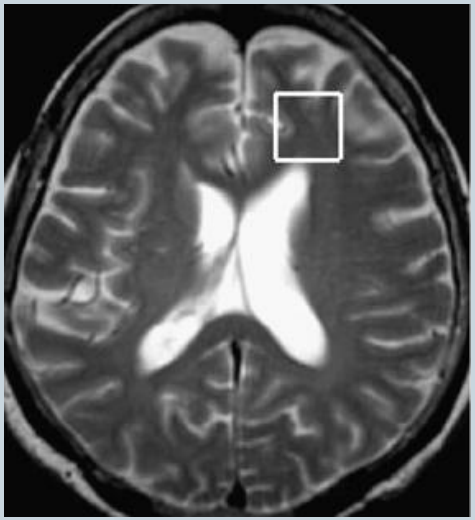
	Early-onset ($n = 20$)		Late-onset ($n = 27$)	
	mean	SD	mean	SD
Age, years	62.7	6.7	65.6	5.4
Age at onset of depression, years	39.7	8.8	60.3	6.9**
^{1}H-MRS findings				
NAA/Cr value	2.15	0.28	1.86	0.21**
Cho/Cr value	1.36	0.15	1.32	0.15
Neuropsychological tests				
Digit Symbol score	43.7	12.9	29.6	9.9**
Trail-Making Part A score	55.7	18.3	74.3	31.9*
Trail-Making Part B score[b]	136.4	59.1	204.4	107.2*
Verbal Associative Fluency score	27.4	8.6	17.3	6.6**
MMSE score	29.3	0.9	28.8	1.7

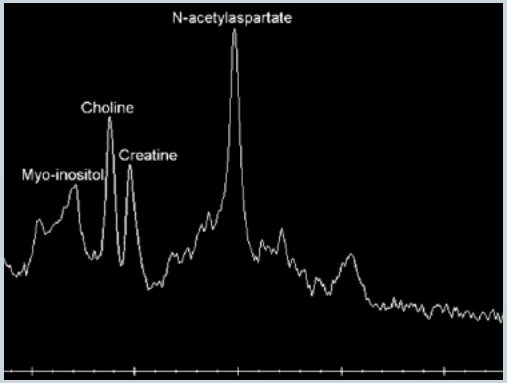
(Murata, Int J Geriat Psychiatry, 2001)

Abnormal Brain Metabolite Level in LLD

Proton magnetic resonance spectroscopy of late-life major depressive disorder

Cheng-Sheng Chen[a,b,c,1], I-Chan Chiang[d,1], Chun-Wei Li[e], Wei-Chen Lin[d], Chia-Ying Lu[d], Tsyh-Jyi Hsieh[d], Gin-Chung Liu[d,f], Hsiu-Fen Lin[g], Yu-Ting Kuo[d,f,*]





Ratios of metabolite levels of MRS in elderly patients with major depression and comparison subjects using ANCOVA controlling for age.

Brain regions and metabolic ratios	Unmedicated major depression $N=18$	Medicated major depression $N=9$	Comparison subjects $N=19$	Analysis $F_{2,43}$	Analysis $P<$	Post hoc comparison#
Frontal white matter						
NAA/tCr	1.35 (0.09)	1.42 (0.09)	1.53 (0.24)	4.30	0.02	U<C
Choline/tCr	1.01 (0.15)	0.90 (0.09)	0.95 (0.19)	1.77	0.18	
Myo-inositol/tCr	0.65 (0.25)	0.58 (0.08)	0.73 (0.23)	1.33	0.27	
Periventricular white matter						
NAA/tCr	1.37 (0.11)	1.40 (0.12)	1.43 (0.12)	1.36	0.27	
Choline/tCr	0.88 (0.09)	0.89 (0.15)	0.86 (0.08)	0.41	0.67	
Myo-inositol/tCr	0.53 (0.11)	0.56 (0.12)	0.49 (0.15)	0.80	0.45	
Basal ganglia						
NAA/tCr	1.41 (0.20)	1.40 (0.10)	1.46 (0.15)	0.44	0.65	
Choline/tCr	0.88 (0.13)	0.85 (0.15)	0.74 (0.19)	3.32	0.046	U>C
Myo-inositol/tCr	0.65 (0.14)	0.56 (0.29)	0.42 (0.26)	4.02	0.025	U>C

(Chen, Psychiatry Research: Neuroimaging 2009)

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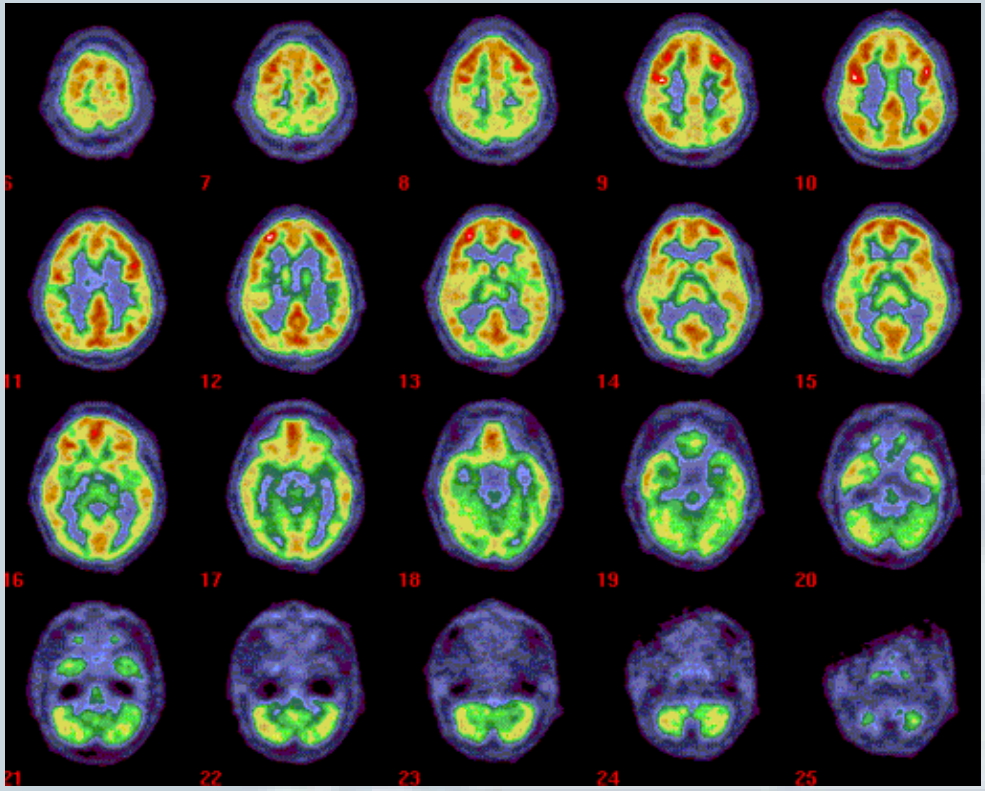


Cerebral Blood Flow in LDD

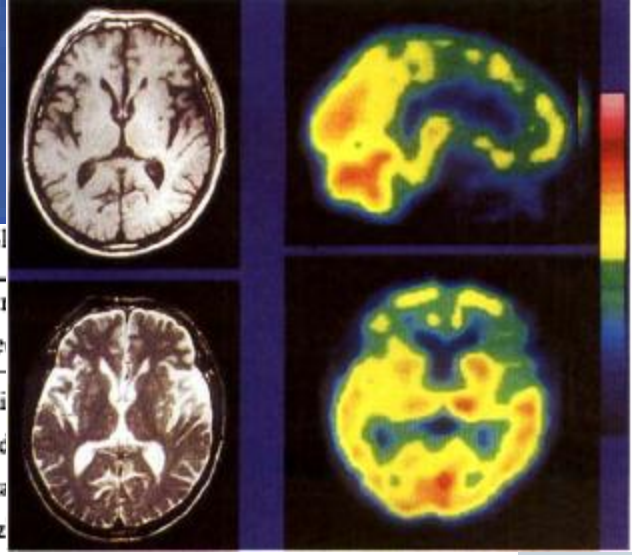
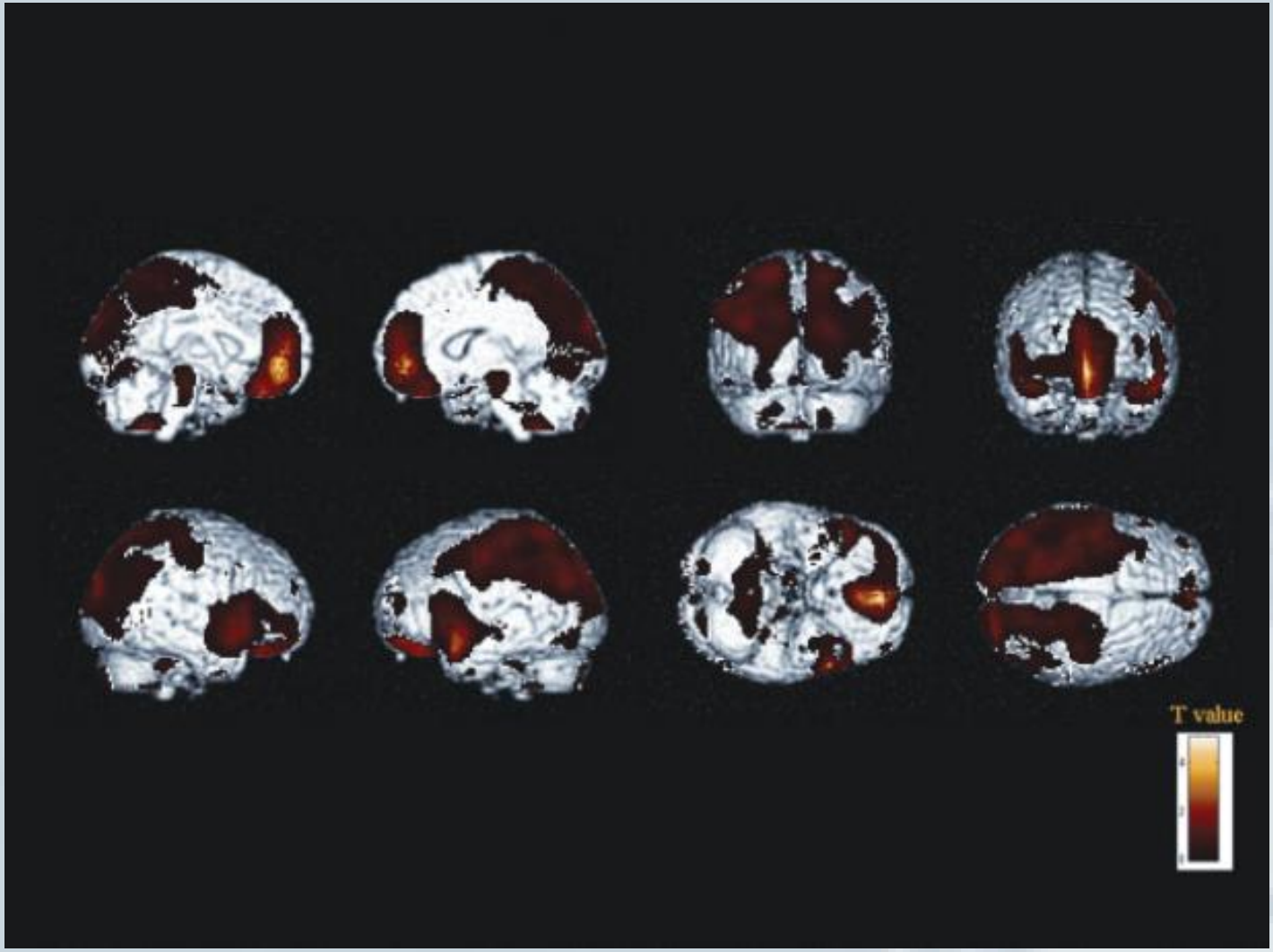


Table 6. Summary of single photon emission computed tomography studies on cerebral blood flow in late-l

Reference	Radiotracer	Patients* No.	Controls No.	CBF at r compare	
Gustafson *et al.* [28]	^{133}Xe	19 (60.0 ± 14)	22 (28.0 ± 7.3)	No signi	
Upadhaya *et al.*[29]	^{99m}Tc-HMPAO	18 (77 ± 7.8)	12 (74.7 ± 9.8)	Interme in tot in Alz patients and in control subjects	
Curran *et al.*[30]	^{99m}Tc-exametazime	20 (70 ± 6.3)	30 (67.1 ± 6.2)	Reduction in anterior cingulate, temporal and frontal cortex and in caudate and thalamus in men only	–
Lesser *et al.*[31]	^{99m}Tc-HMPAO ^{133}Xe	39 (60.9 ± 8.1)	20 (69.1 ± 6.5)	Reduction in global flow, orbital frontal and inferior temporal regions	No clear correlation
Ito *et al.*[32]	^{99m}Tc-HMPAO	Unipolar: 11 (66.6 ± 7.1) Bipolar: 6 (66.7 ± 5.8)	9 (65.7 ± 10.5)	Reduction in prefrontal cortices, limbic systems and paralimbic areas in both depression groups	–
Present study	^{99m}Tc-HMPAO	18 (66.2 ± 7.3)	13 (66.4 ± 7.8)	Reduction in anterior cingulate gyrus, prefrontal cortex, temporal cortex, parietal cortex, hippocampus and caudate nucleus.	No correlation

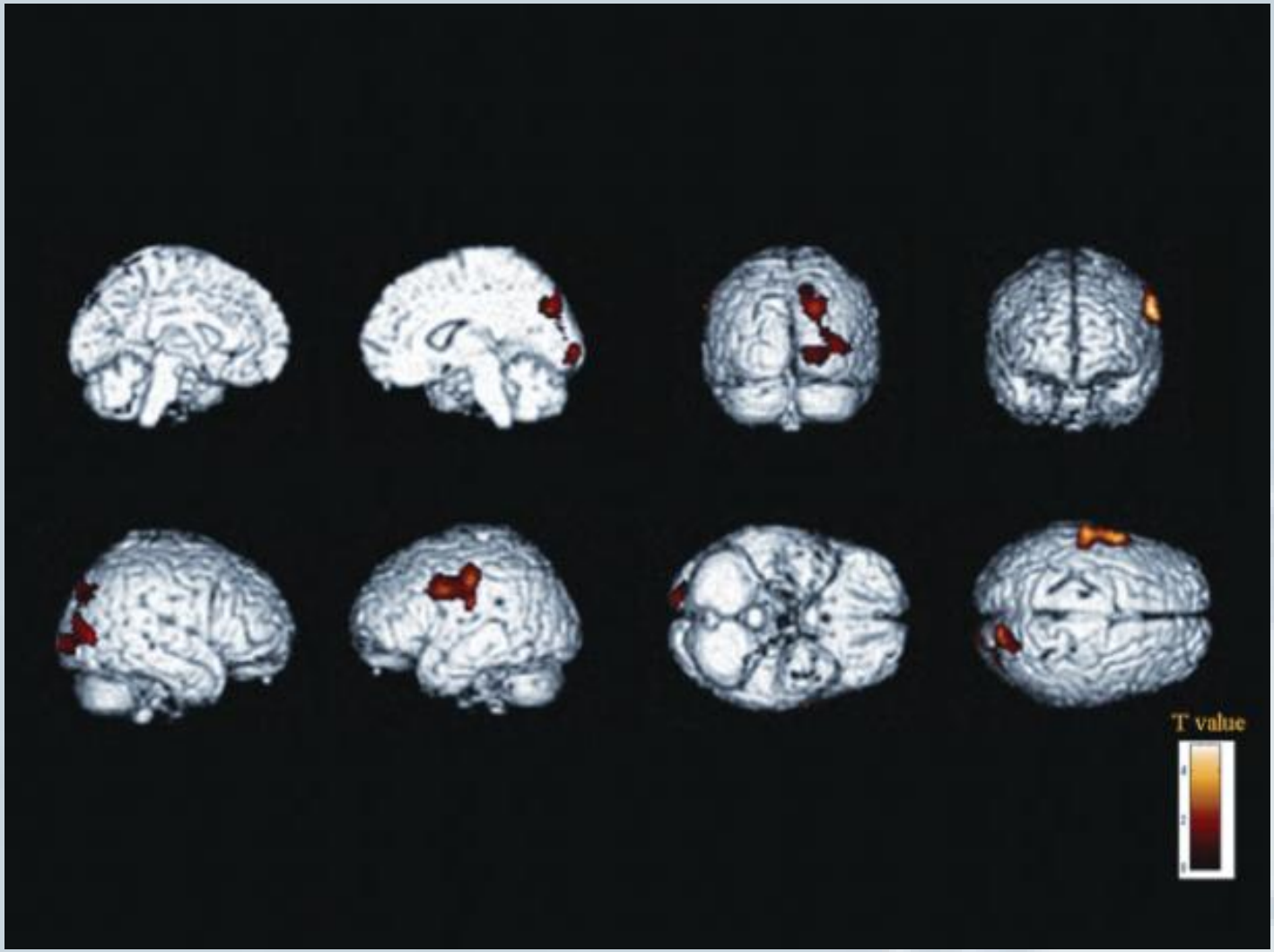
(Awata, Psychiatry and Clinical Neurosciences, 1998)

Cerebral Blood Flow in LDD: Baseline



(Junko, Int J Geriatr Psychiatry, 2008)

Cerebral Blood Flow in LDD: After treatment



(Junko, Int J Geriatr Psychiatry, 2008)

Cerebral Blood Flow and Refractoriness

Table 4. Comparison of relative regional cerebral blood flow between patients with refractory and non-refractory late-life depression and controls

Regions of interest	Refractory	Non-refractory	Controls
Pons	0.78 ± 0.06	0.78 ± 0.05	0.08 ± 0.03
Midbrain	0.78 ± 0.04	0.80 ± 0.10	0.81 ± 0.05
Cerebellar vermis	0.99 ± 0.02	0.99 ± 0.04	0.98 ± 0.04
Cerebellar hemisphere	1.00 ± 0.00	0.99 ± 0.00	1.00 ± 0.00
Anterior cingulate gyrus	0.73 ± 0.05***†	0.80 ± 0.04	0.85 ± 0.05
Superior frontal gyrus	0.77 ± 0.04***†	0.84 ± 0.05	0.87 ± 0.05
Middle frontal gyrus	0.78 ± 0.06**	0.83 ± 0.05	0.85 ± 0.04
Inferior frontal gyrus	0.76 ± 0.05**†	0.83 ± 0.05	0.85 ± 0.05
Precentral gyrus	0.77 ± 0.04**	0.81 ± 0.06	0.83 ± 0.04
Postcentral gyrus	0.76 ± 0.05**	0.81 ± 0.05	0.83 ± 0.04
Hippocampal gyrus	0.73 ± 0.06*	0.76 ± 0.03	0.78 ± 0.04
Superior temporal gyrus	0.79 ± 0.06**	0.83 ± 0.06	0.87 ± 0.04
Middle temporal gyrus	0.83 ± 0.06*	0.85 ± 0.06	0.87 ± 0.03
Inferior temporal gyrus	0.78 ± 0.05*	0.80 ± 0.05	0.83 ± 0.04
Superior parietal lobule	0.77 ± 0.04	0.75 ± 0.11	0.80 ± 0.06
Supramarginal gyrus	0.79 ± 0.05**	0.82 ± 0.05	0.86 ± 0.05
Angular gyrus	0.79 ± 0.04*	0.79 ± 0.06	0.84 ± 0.04
Lateral area of occipital	0.77 ± 0.03	0.80 ± 0.04	0.82 ± 0.07
Posterior area of occipital	0.77 ± 0.06*	0.83 ± 0.06	0.85 ± 0.08
Occipital cuneus	0.89 ± 0.04	0.91 ± 0.05	0.93 ± 0.07
Caudate nucleus	0.85 ± 0.07**	0.86 ± 0.10*	0.95 ± 0.05
Lentiform nucleus	0.93 ± 0.08	0.97 ± 0.08	0.97 ± 0.05
Thalamus	0.89 ± 0.06	0.92 ± 0.07	0.94 ± 0.06
Semiovale center	0.67 ± 0.07	0.69 ± 0.93	0.72 ± 0.07

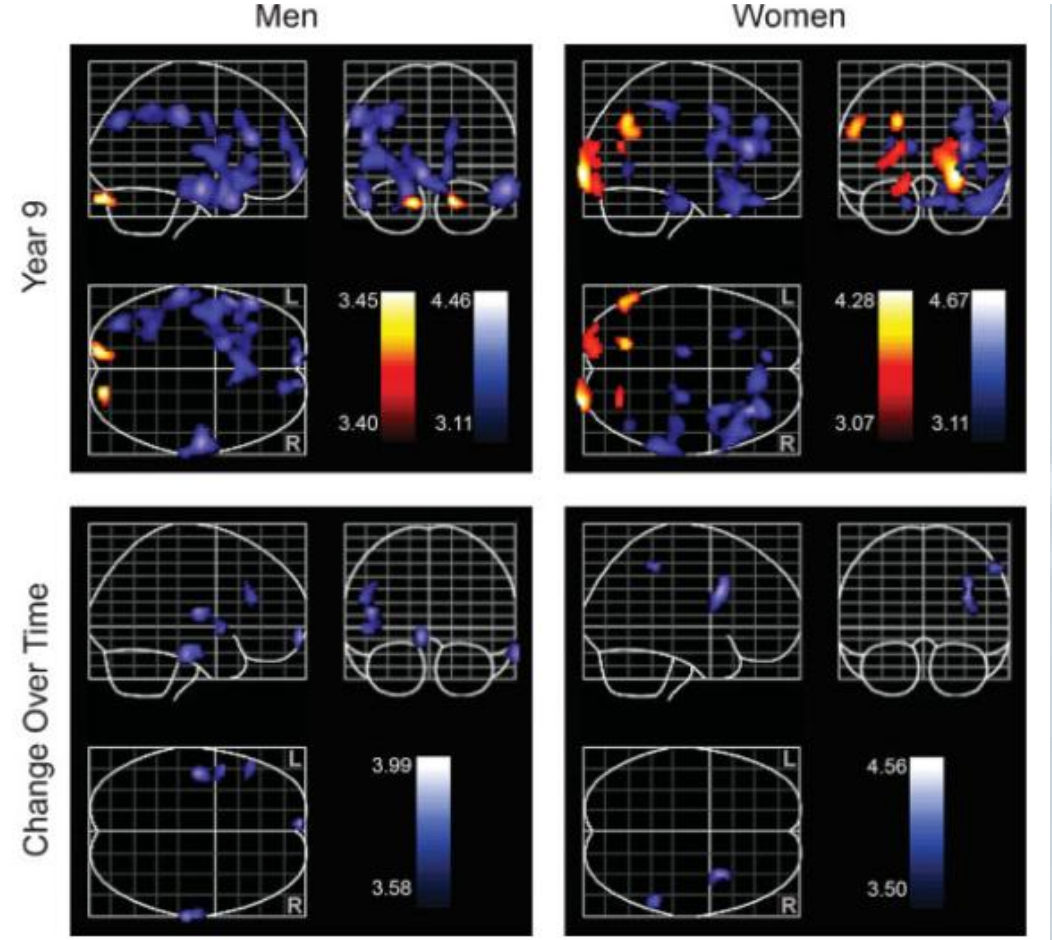
Values are the mean ± SD ^{99m}Tc uptake ratios to cerebellum (CBF/C). ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$ compared with control; †$P < 0.05$ compared with non-refractory depression.

(Awata, Psychiatry and Clinical Neurosciences, 1998)

Cerebral Blood Flow in LDD

Longitudinal study of chronic depressive symptoms and regional cerebral blood flow in older men and women

Vonetta M. Dotson[1*], Lori Beason-Held[1], Michael A. Kraut[2] and Susan M. Resnick[1]



(Dotson, Int J Geriatr Psychiatry 2009)

5-HT1A Receptor and LLD

Serotonin 1A Receptor Binding and Treatment Response in Late-Life Depression

Carolyn Cidis Meltzer*[1,2,3], Julie C Price[1], Chester A Mathis[1], Meryl A Butters[2], Scott K Ziolko[1], Eydie Moses-Kolko[2], Sati Mazumdar[2,4], Benoit H Mulsant[2], Patricia R Houck[2], Brian J Lopresti[1], Lisa A Weissfeld[4] and Charles F Reynolds[2,3,5]

Table 2
Patients

Region		mean
DRN		62
LOF		241
PGC		51
SGC		47
HIP		24
MTC		40
OCC		92

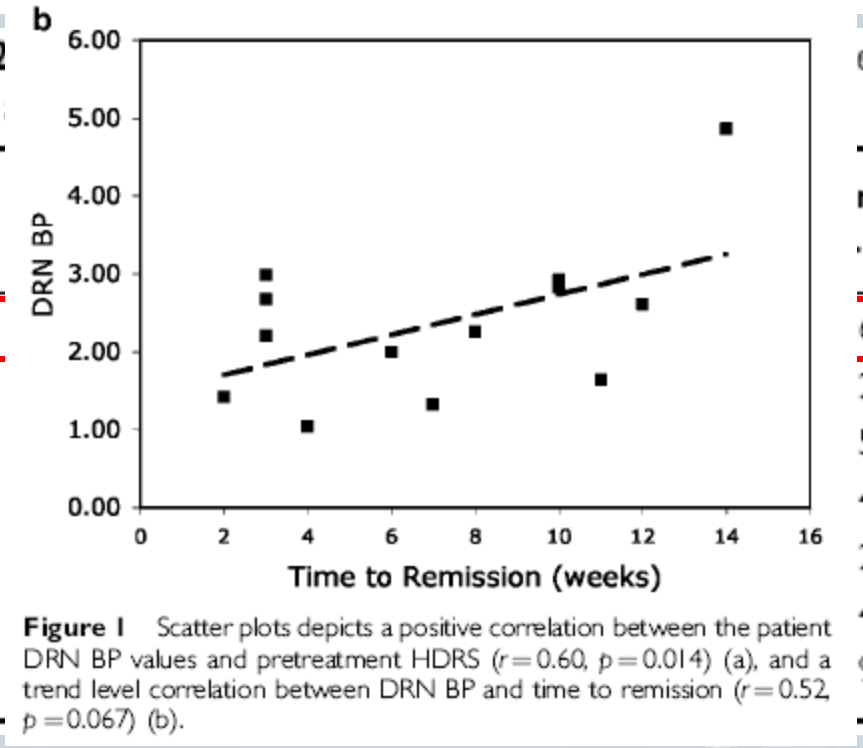
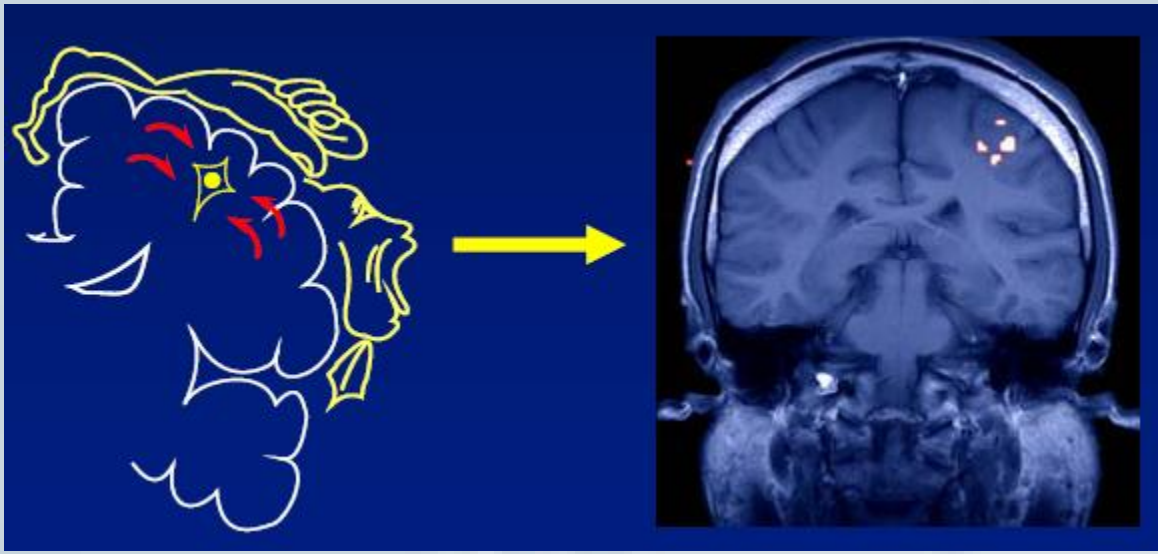


Figure 1 Scatter plots depicts a positive correlation between the patient DRN BP values and pretreatment HDRS ($r = 0.60$, $p = 0.014$) (a), and a trend level correlation between DRN BP and time to remission ($r = 0.52$, $p = 0.067$) (b).

(Meltzer, Neuropsychopharmacology 2004)

Neuroimaging Concepts

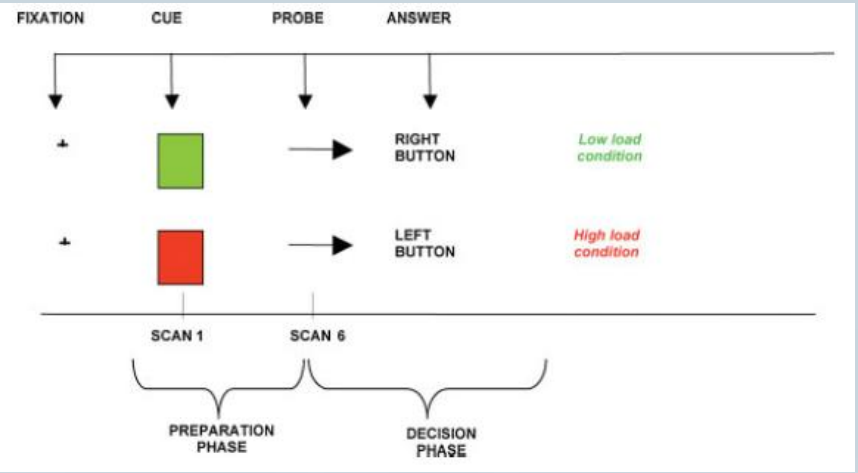
- Structural Imaging
  - MRI (White Matter Lesions)
  - Diffusion Tensor Imaging
  - MR Spectroscopy
- **Functional Imaging**
  - SPECT
  - PET
  - fMRI

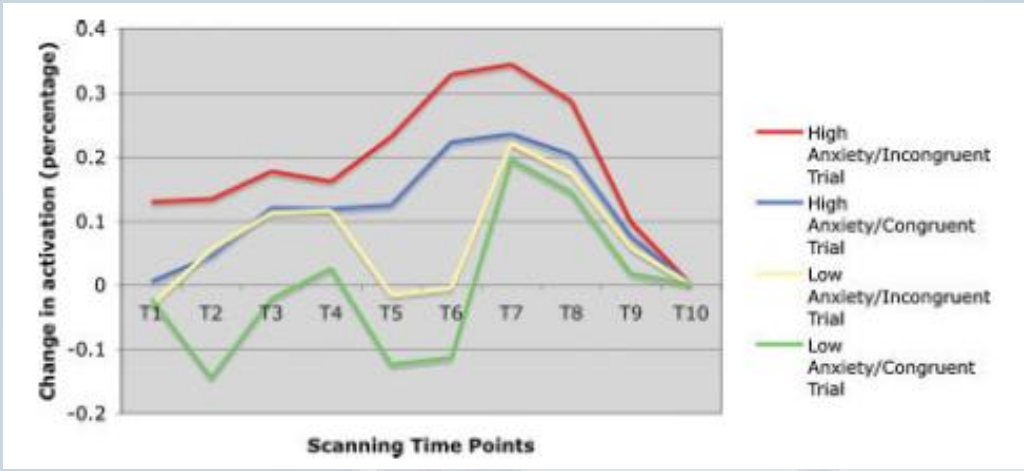


fMRI activation in LL anxious Depresson

fMRI activation in late-life anxious depression: a potential biomarker

Carmen Andreescu[1], Meryl Butters[1], Eric J. Lenze[2], Vijay K. Venkatraman[3], Megan Nable[4], Charles F. Reynolds III[1] and Howard J. Aizenstein[1,3]*



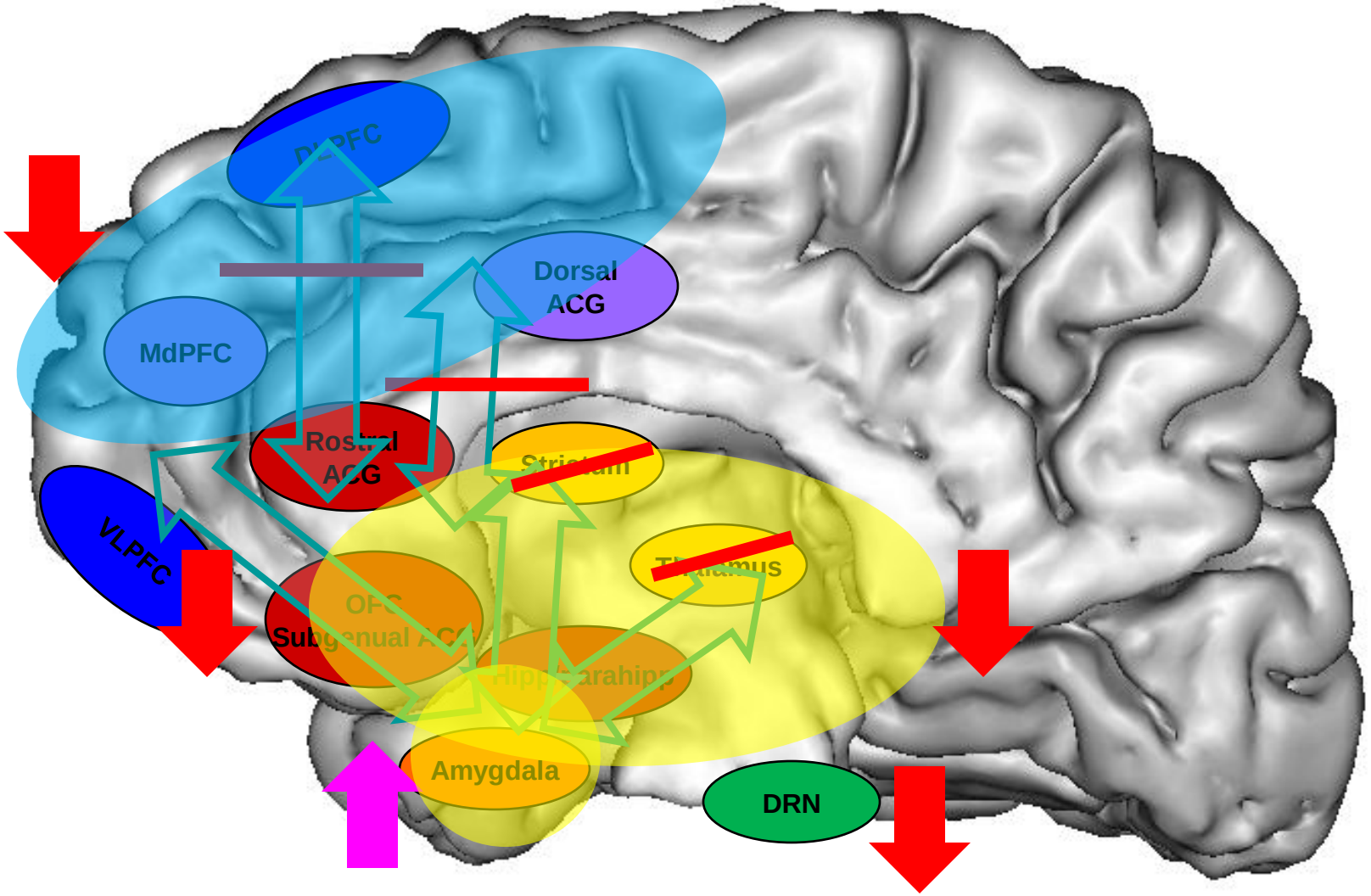


(Aindreescu, Int J Geriatr Psychiatry, 2009)

Neuroimaing in the Assessment of LLD

- **Possible Role as Diagnostic Biomarker for LLD ?**
  - Diagnosis of Vascular Depression based on MRI findings
- **Decision of a subtype of LLD**
  - Older age of depression onset
  - Decreased family history of mental illness
  - Poor executive function task
- **Prediction of treatment response**
  - Prefrontal atrophy associated with Tx response of rTMS (Lt DLPFC)
  - Predictive Power of treatment efficacy ???
- **Potential for achieving more personalized diagnosis and treatment in LLD**

Limbic-Cortical Dysregulation: Model of Depression



감사합니다!