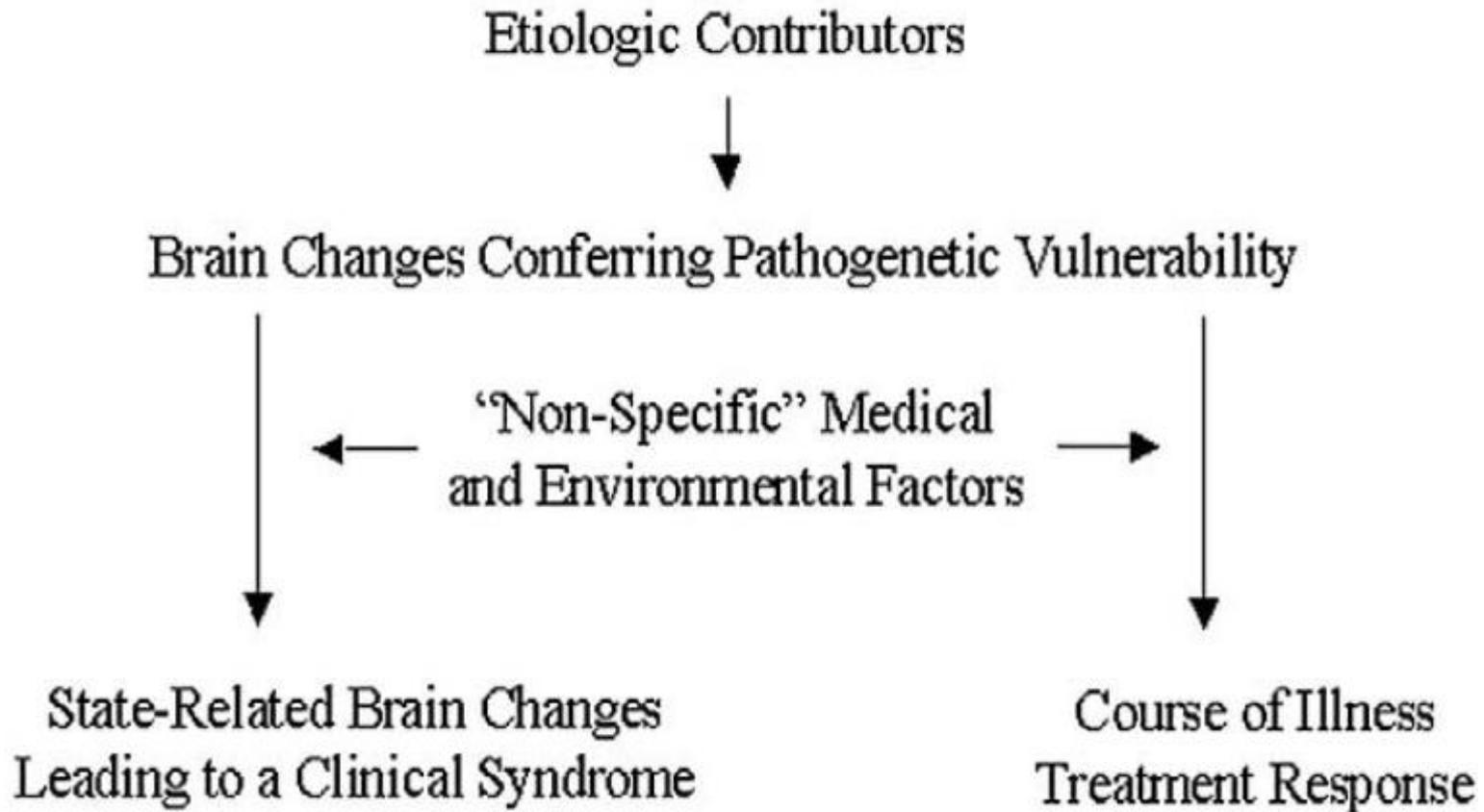


노년기 우울증의 뇌영상 지표

이하의대 정신과
배재남

Model for Late-life Psychiatric Disorders

(Alexopoulos GS, 2005)



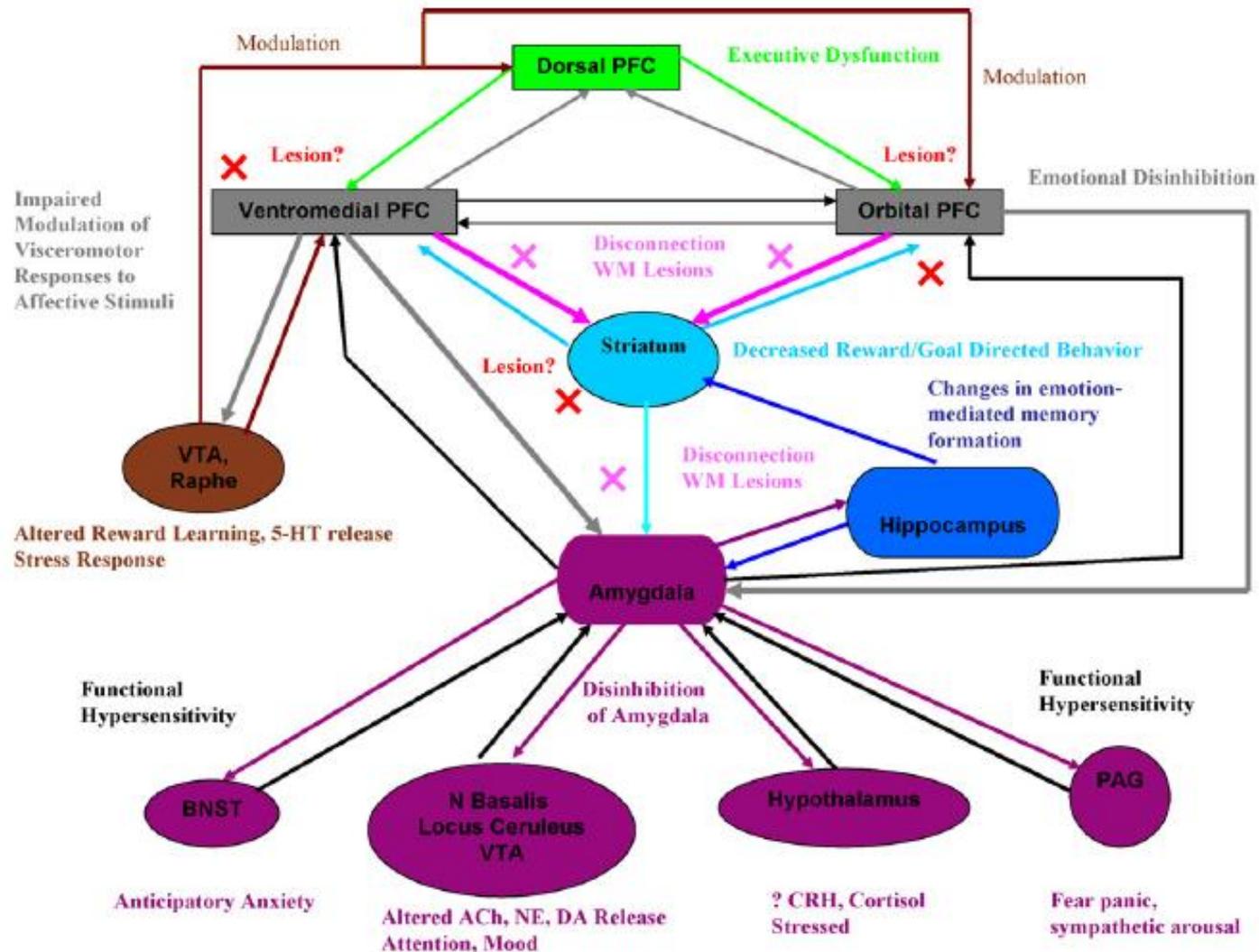
Fronto - Striatal - Limbic Functions

(Alexopoulos GS, 2005)

- Fronto-striatal dysfunction
- Amygdalar dysfunction
- Hippocampal dysfunction
 - ➔ Morbid vulnerability
 - Not final mechanism !!
- Caused by Various processes :
 - Genetic / Vascular/ Immune / Inflammatory,
 - Neurochemical / Neurodegenerative,
 - Other aging-related factors,

Amygdala-centric Model

J. Savitz, W.C. Drevets / Neuroscience and Biobehavioral Reviews 33 (2009) 699–771



Structural Imaging

2 Lines of Research

- Gray matter volumes
- White matter hyperintensities
 - Periventricular hyperintensities (PVH)
 - Deep white matter hyperintensities (DWMH)
 - Subcortical gray matter hyperintensities (SCH)
- Methods
 - MRI,
 - DTI (Diffusion Tensor Imaging)
 - MTR (Magnetization transfer ratio) imaging

Volumetric Findings

- Decreased gray matter volumes
 - Prefrontal, anterior cingulate, orbitofrontal cortex, hippocampus, amygdala, basal ganglia
- Decreased hippocampal volume
 - Associated with later age of onset, vascular risk factors, repeated episode of depression
 - Atrophic changes ↑ : poorer treatment outcome
- Antidepressants may reverse some of volume reductions ??

PVWML and DWML

- Fazekas : ‘Continuity (to ventricle) Rule’
- Smooth PVWML (including caps & halos)
 - Non ischemic (ependymal loss, myelination in adjacent fiber tract)
 - Wallerian degeneration
 - Increase of interstitial fluid
- DWML & Irregular PVWML: Ischemic
 - Irregular PVWML: by chronic hemodynamic insufficiency
 - DWML : by small vessel disease

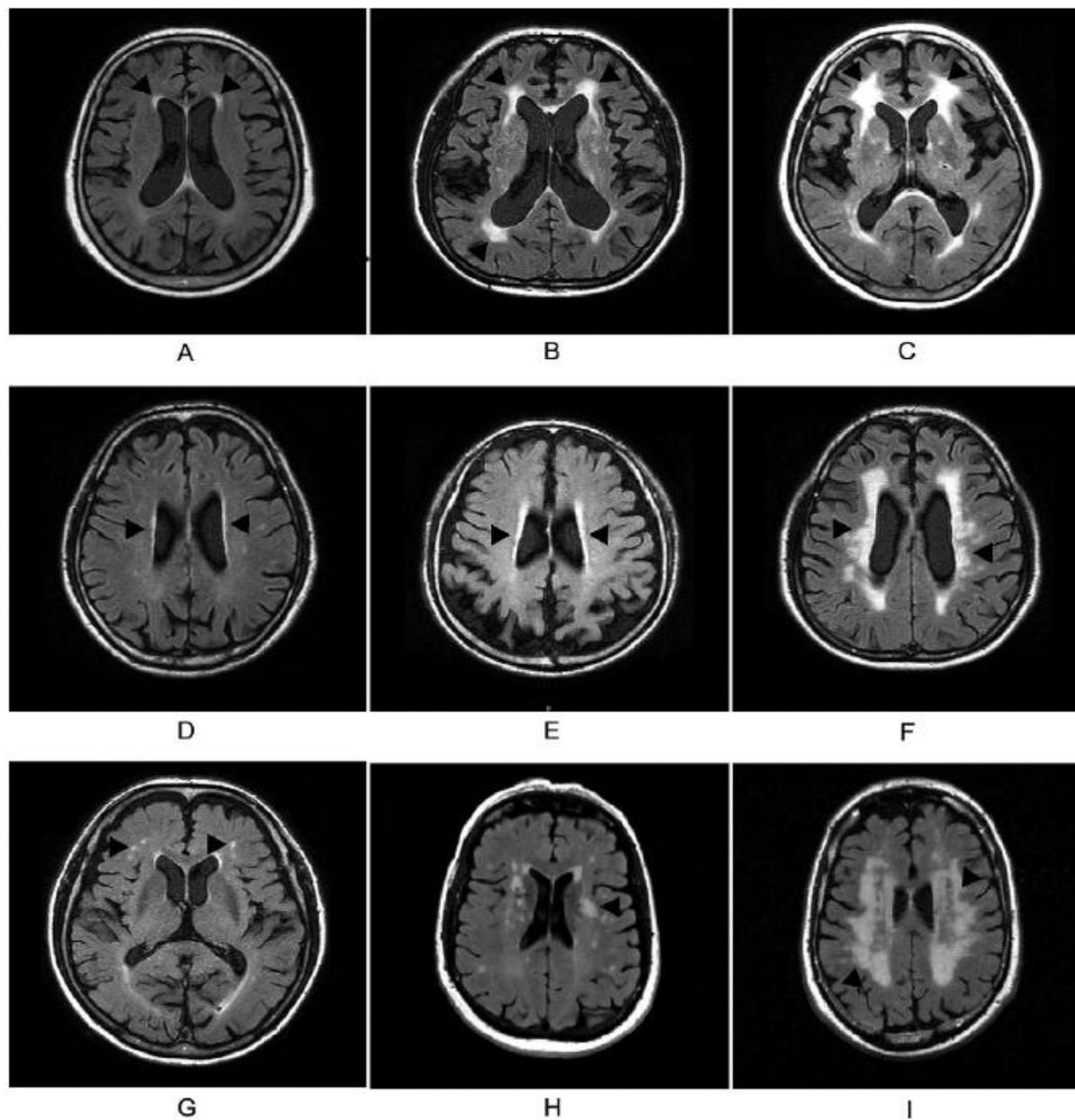


Figure 1. Forms of white matter lesions (WML); small caps (A), large caps (B), extending caps (C), thin lining (D), smooth halo (E), irregular periventricular WML (F), punctuate deep WML (G), deep WML beginning confluence (H), and confluent deep WML (I).

Volume & Severity of PVH, DWMH

- Greater DWMH & PVH in first onset of major depression over age 50 than earlier onset
- Greater DWMH : poorer response to treatment and increased mortality
 - Higher HAM-D
 - Lower MMSE
 - More severe longitudinal course
 - Chronicity or relapse of depression
 - Poor outcomes

SCHs

- Late life depressives :
 - Greater severity and volume of SCHs
- SCHs
 - Psychomotor slowing
 - Executive dysfunctions
- Not differ between early onset and late onset depressives ??

Locations of WMH

- Frontal lobe
 - Particularly associated with late life depression
 - Bilateral frontal region
 - Left parieto-temporal region
 - Medial orbital region
 - Rt superior frontal gyrus
- Anterior cingulate
- Disrupting frontal-subcortical pathways :
chronicity & cognitive impairment in late life
depression

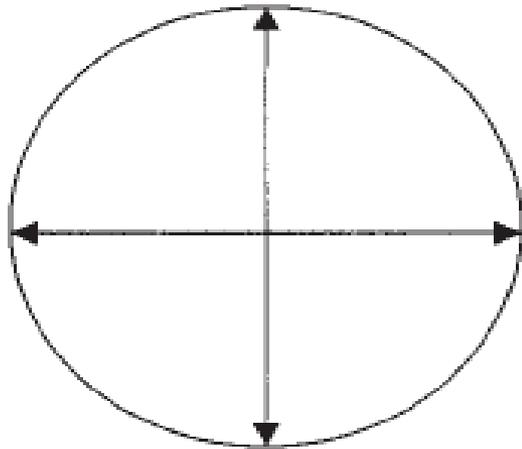
Diffusion Tensor Imaging (DTI)

- Diffusion Weighted Image of MRI
- MRI scanners equipped to perform echo-planar imaging
- Measure the diffusion of water molecule (Brownian motion)
- Identifying cerebral white matter and neural fiber tracts, studying neural circuitry
- Surrogate marker of tissue structural integrity

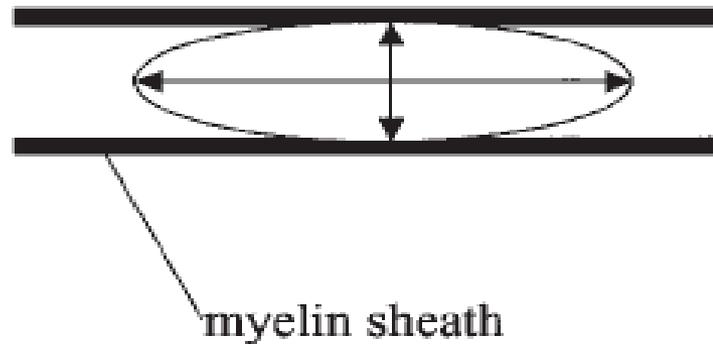
➔ Tractography

Isotropic & Anisotropic Diffusion

unrestricted (isotropic)
diffusion

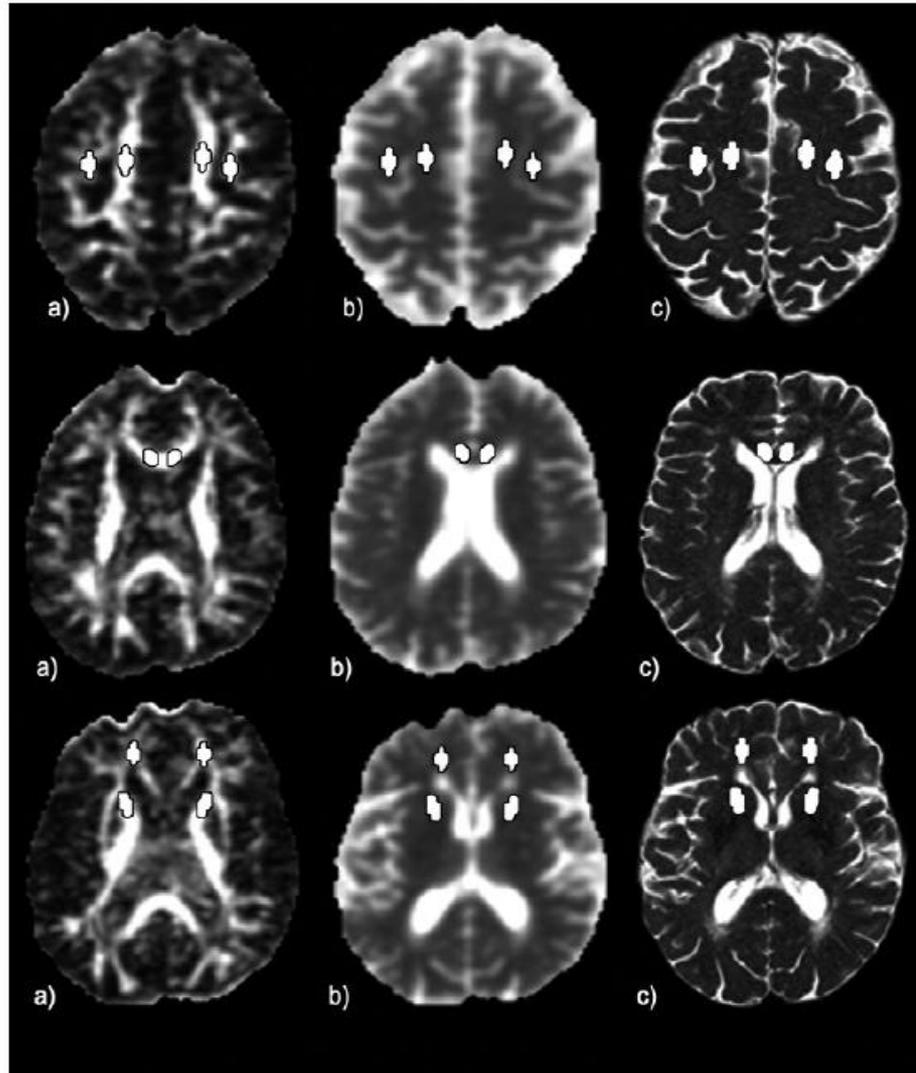


restricted (anisotropic)
diffusion



DTI Findings in Late Life Depression

(Bae JN et al, 2006)

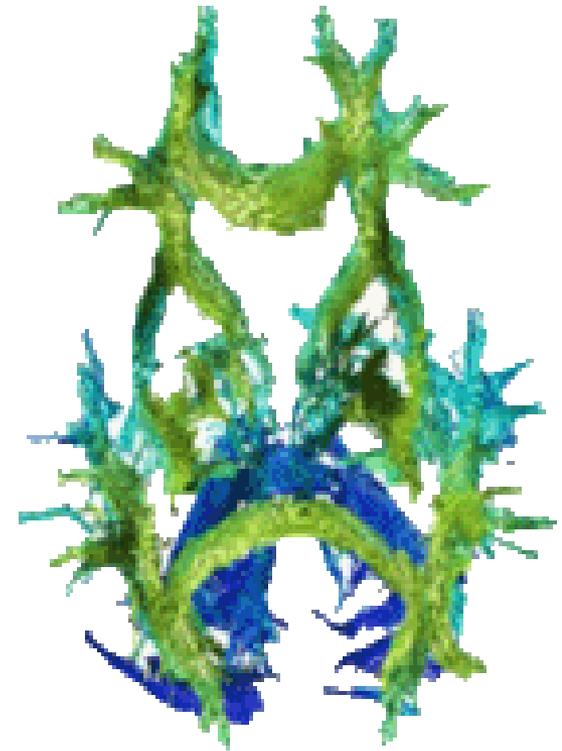
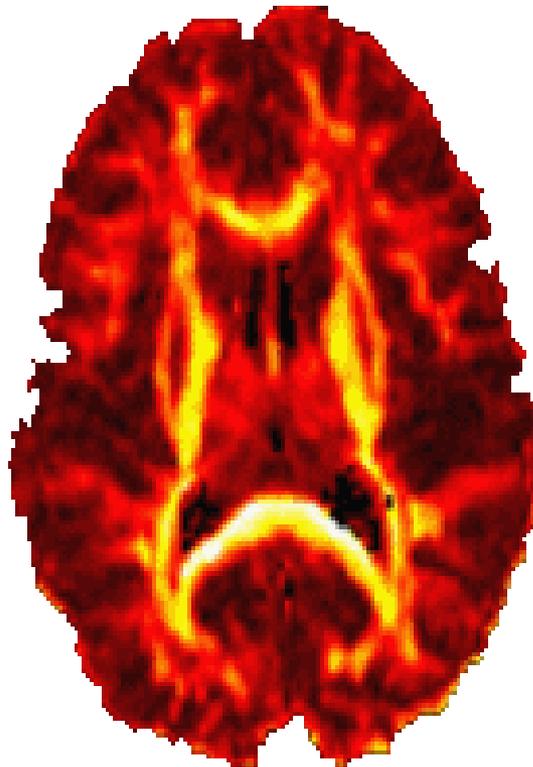
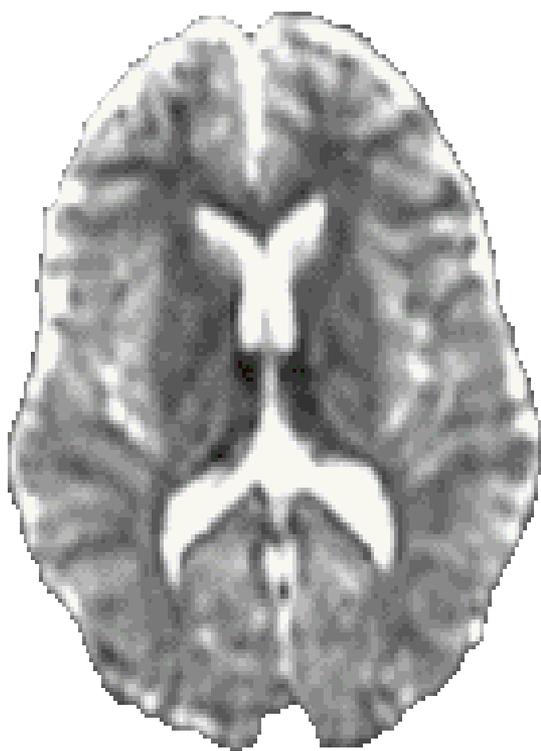


(Dorsolateral PFC*)

(Corpus Callosum)

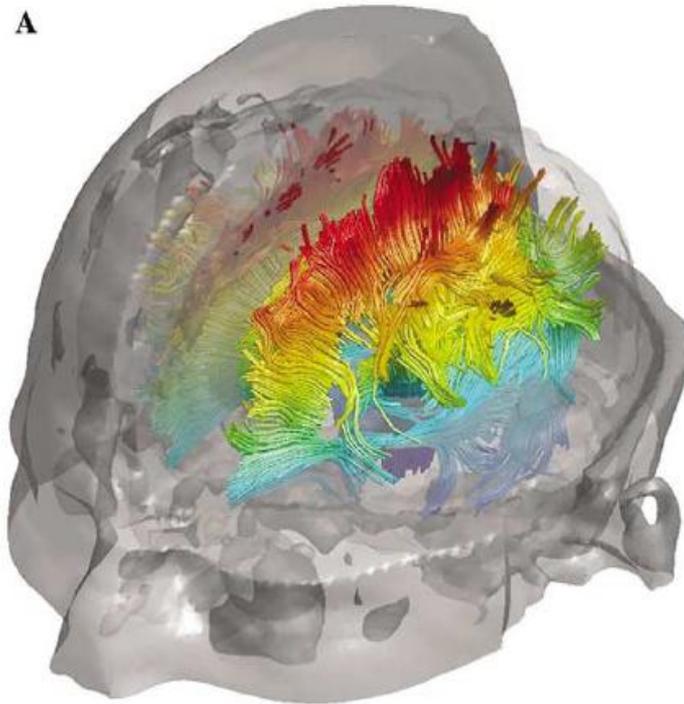
(Ant Cingulate*, Internal Capsule)

Images, curtsey of Dr. E Hsu, Duke University Medical Center



Images, curtesy of Dr. WD Taylor, Duke University Medical Center

A



B



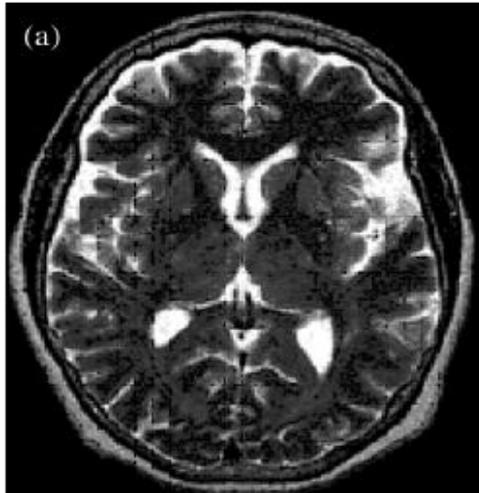
Magnetization Transfer MRI

- The transfer from bound water to free water
- Particularly sensitive to detecting changes in myelin-related proteins in white matter
- Late life depression (Gunning-Dixon FM, 2008)
 - Impaired integrity of myelin in fronto-striato-limbic circuits
- Higher white matter lesion load in nondepressed individuals, after 4 yr f/u (Godin O, 2008)
 - Increased risk of developing depression

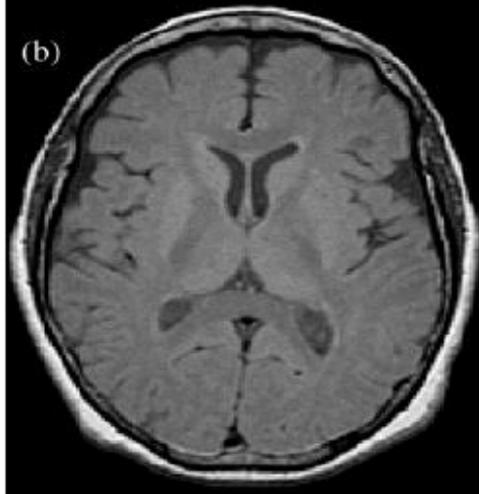
MT MRI

A. Kumar et al. / Psychiatry Research: Neuroimaging 130 (2004) 131–140

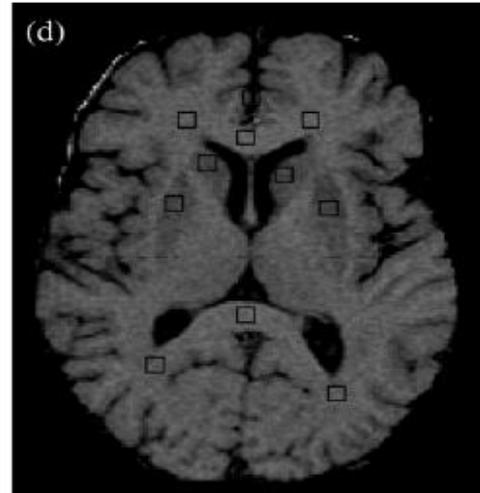
(T2 weighted)



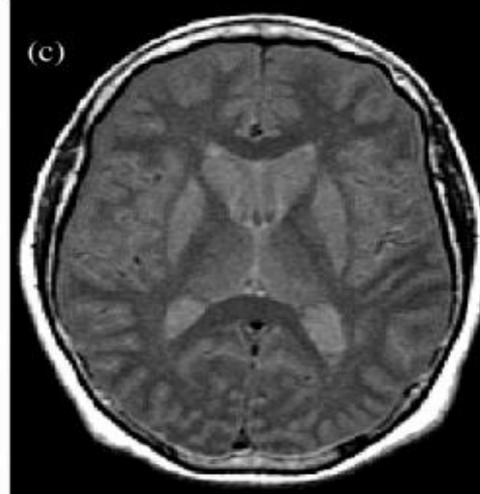
(PD weighted image without the off-resonance pulse)



(MT ratio Image)



(Image with the off-resonance pulse)



Functional Imaging

SPECT in LLD

- Reduced perfusion in late life depression (LLD)
 - Temporal lobe,
 - Left frontal region,
 - Anterior cingulate and prefrontal cortex
- Lt frontal region hypoperfusion
 - Can reverse with successful antidepressants (Navarro, 2002)
 - May persist even after remission (Kimura, 2003)

PET in LLD

- Conducted mainly in pts with midlife depression
- Mainly focusing on serotonin receptors
- Loss of 5-HT_{2A} receptors in aging
 - No difference in late-life depression compared control, But ↓ in AD (Meltzer, 1999)
- Binding ↓ of 5-HT_{1A} autoreceptor in dorsal raphe nucleus (Meltzer, 2004)
 - Depression severity ↑,
 - Predictive to treatment to SSRIs

Functional MRI in LLD (I)

- Larger literature on late-life depression
- Relationships between cognition and mood
- Executive & affective task (Gunning-Dixon, 2005)
 - Less activation of dorsal anterior cingulate
 - Greater activation of the subgenual & dorsomedial prefrontal cortex
- Verbal fluency test (de ASIS, 2001)
 - Bilateral hypoactivation of the dorsal anterior cingulate & hippocampus

Functional MRI in LLD (II)

- Explicit sequence learning (Aizenstein, 2005)
 - prefrontal activation ↓ , caudate activation ↑
- Episodic memory (Gron, 2002)
 - ↓ activation of temporo-limbic structures (↑ than AD)
- LLD (Aizenstein, 2005)
 - Hypoactivation of DLPFC & ACC, decreased functional connectivity between 2 regions
 - Following 12wks paroxetine :
 - Resolved hypoactivation,
 - But, decreased functional connectivity persisted

Functional MRI in LLD (III)

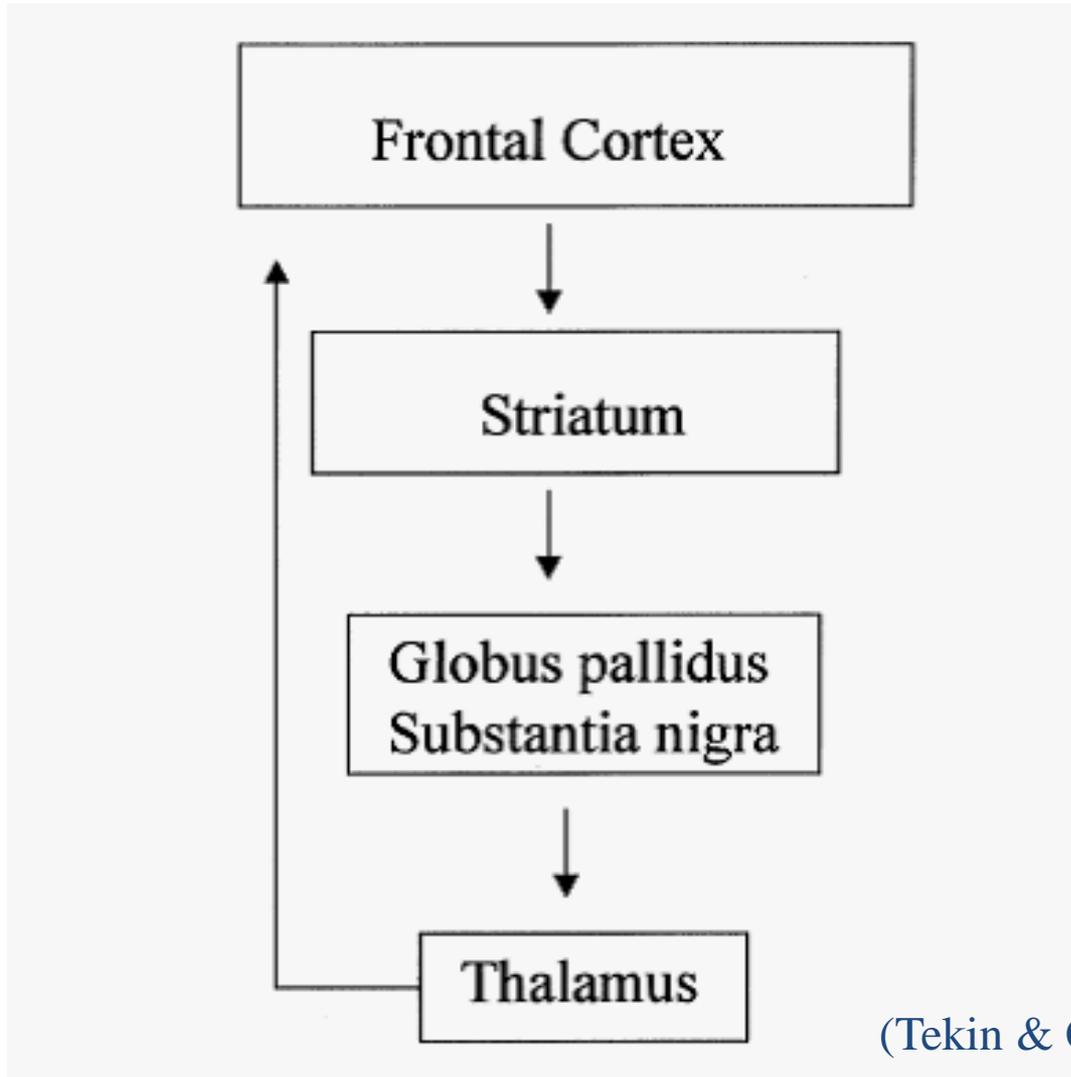
- In summary (Smith GS et al, 2007),
- Geriatric depression
 - Not only, specific regions of fronto-striatal & fronto-limbic networks exhibits abnormal activation.
 - But also, a disconnection syndrome affecting these systems may exist.

Vascular Depression in Late- life Depression

Frontal Subcortical Circuits

- ‘**Vascular depression**’ : late onset depression
 - Clinical Sx & Sg (Alexopoulos, 1997)
 - Neuroradiological feature (Krishnan, 1977)
- ‘**Depression–executive dysfunction syndrome**’ (Alexopoulos, 2001)
 - Impairment of brain function, regardless etiology
- ‘**Subcortical ischemic depression**’ (Krishnan, 2004)
 - Concept of subcortical ischemic vascular dementia

Frontal Subcortical Circuits



(Tekin & Cummings, 2002)

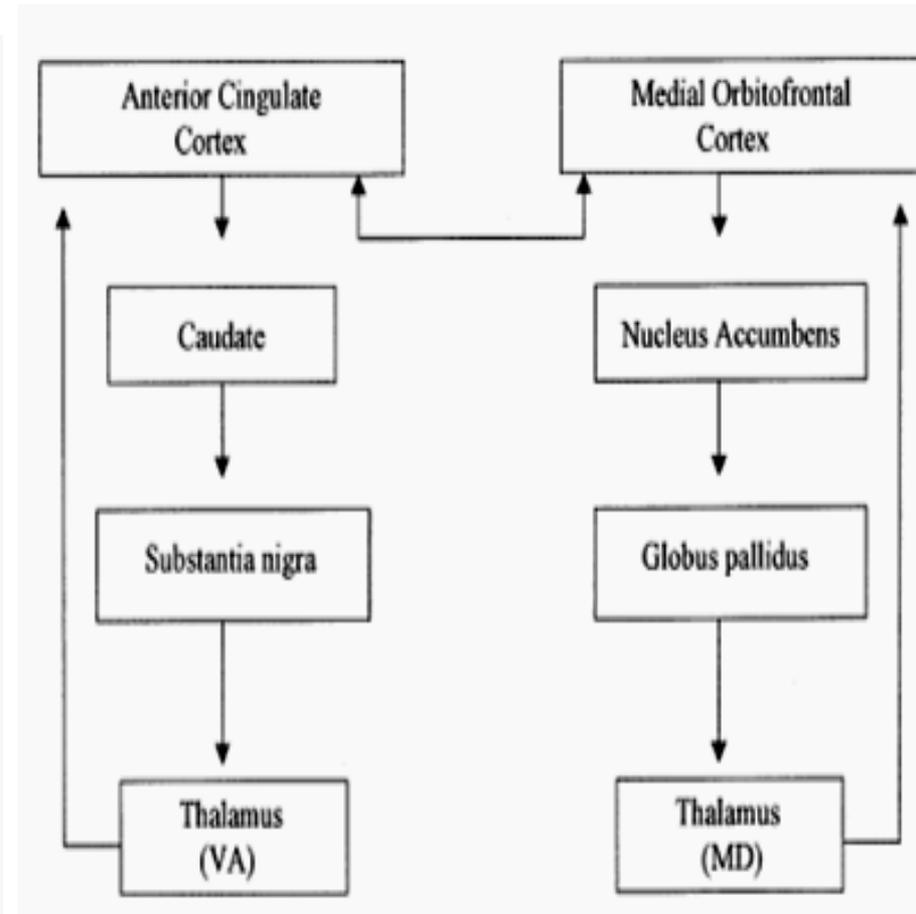
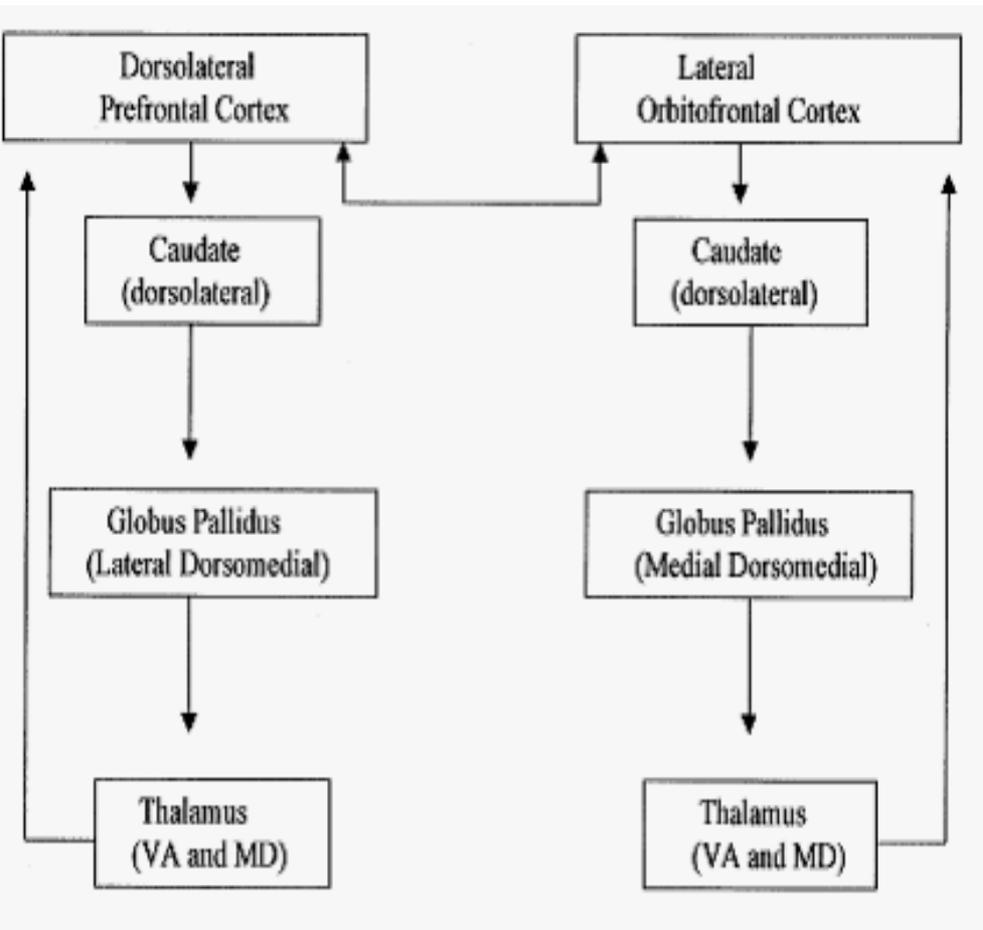
Frontal Subcortical Circuits

Executive
dysfunction

Mood lability
Disinhibition

Apathy

Mood lability
Disinhibition



(Tekin & Cummings, 2002)

Definition of Vas Depression

- Alexopoulos GS (Arch Gen Psy, 1997)
- “Hypothesis”
- Clinical presentation
 - Cardinal features
 - Secondary features

Cardinal Features

- Clinical and/or laboratory evidence of **vascular disease or vascular risk factors**
 - Hx of stroke/TIA, focal neurological sx & sg
 - Atrial fibrillation, angina, hx of MI, carotid bruit, HT, hyperlipidemia
 - Lab : WMH, infarcts, carotid occlusion, stenosis of Willis circle arteries
- Depression **onset after 65 yrs**, or change in the course of depression after the onset of vascular disease in early-onset depression

Secondary Features

- Cognitive impairment
 - Not limited executive dysfunction
- Psychomotor retardation
- Limited depressive ideation, eg, guilt
- Poor insight
- Disability
- Absence of family history of mood disorders

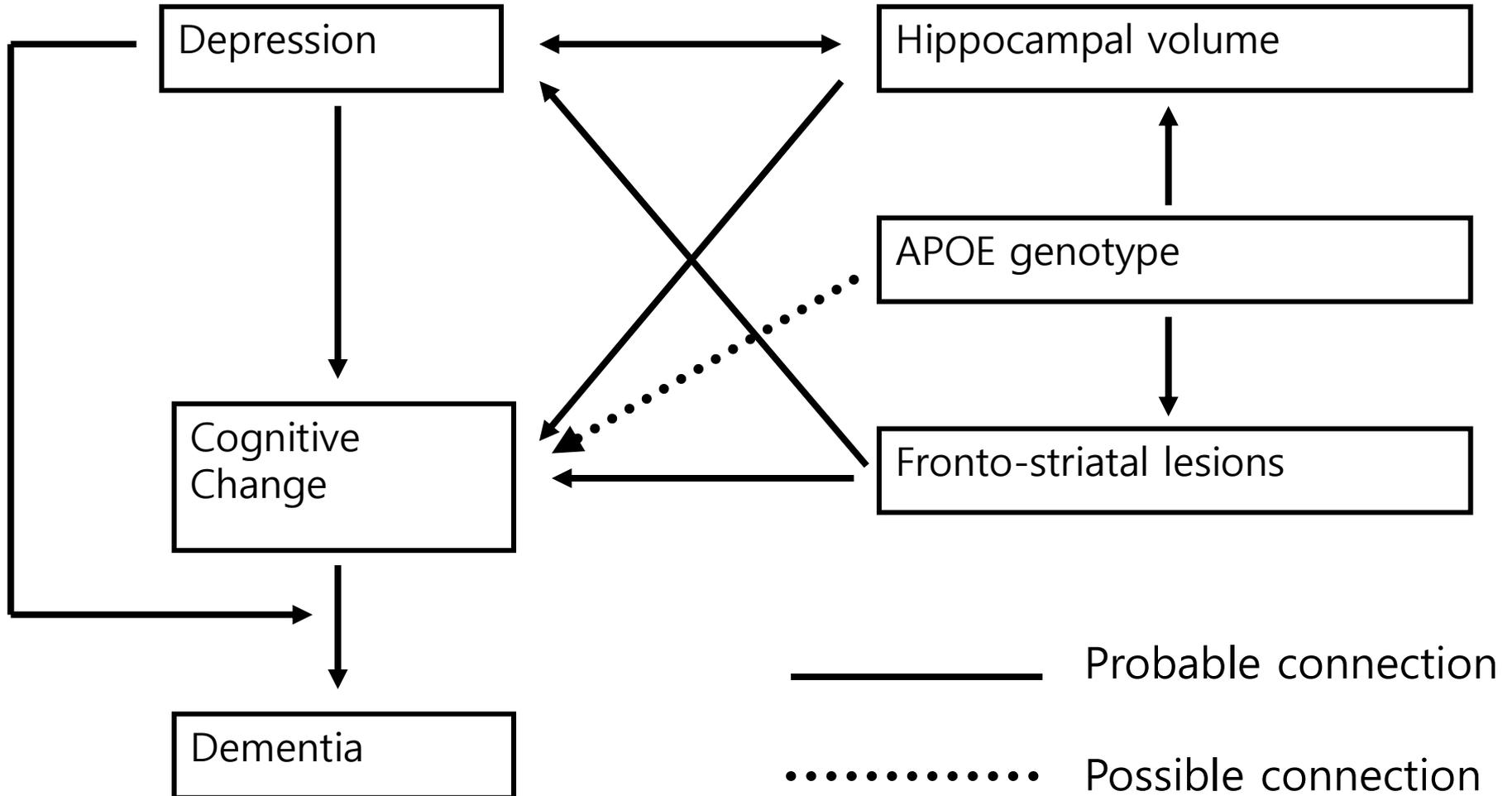
Mechanisms of Vas Depression

- Small lesions disrupting critical pathways
 - Stroke, lacunar infarct (caudate head or Lt. frontal pole)
 - a minority of vascular depression
- Accumulation of lesions exceeding a threshold
 - Most applicable to pts with neurologically silent lesions or old stroke
 - Total area of WMH $> 10 \text{ cm}^2$
 - Vascular risk factors
 - Vulnerability by the lesions or by CV disturbances

Subcortical Ischemic Depression

- Krishnan KRR (2004)
- Criteria for **major depressive episode**
- Evidence for **subcortical ischemic change on neuroimaging**
 - Hyperintense areas on CT, T2 weighted MRI scans (DWMH, SGH)
- The presence of a risk factor for cerebrovascular disease is not required
 - When present, should be specified on axis III
 - HT, coronary artery disease, atrial fibrillation

Conceptual Framework (Krishnan, 2004)



Cause, Clinical Presentation of SID

