Award Number:
DAMD17-99-1-9498

TITLE:

SPECT and fMRI analysis of motor and cognitive indices of early Parkinson's disease: the relationship of striatal dopamine and cortical function

PRINCIPAL INVESTIGATOR:

John D.E. Gabrieli, Ph.D.

CONTRACTING ORGANIZATION:

Rush University Medical Center
Chicago, IL 60612

REPORT DATE:

September 2005

TYPE OF REPORT:

Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT:

χ Approved for public release; distribution unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
September 2005	Final	01 OCT 1999 - 31 AUG 2005

4. TITLE AND SUBTITLE
SPECT and fMRI analysis of motor and cognitive indices of early Parkinson's disease: the relationship of striatal dopamine and cortical function

5a. CONTRACT NUMBER

5b. GRANT NUMBER
DAMD17-99-1-9498

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Glenn T. Stebbins, Ph.D.
John D.E. Gabrieli, Ph.D.

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
. Rush University Medical Center
Chicago, IL 60612

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Parkinsonism is the result of decreased striatal dopamine integrity. Neurotoxins often selectively affect dopamine producing cells and lead to behavioral manifestations of parkinsonism. The effects of parkinsonism is impaired motoric and strategic/working memory cognitive performance. Both motoric and strategic/working memory deficits also increase in community dwelling healthy elderly individuals as age increases, suggesting a link between age-associated parkinsonism and age-associated motoric and cognitive changes. In the present study we sought to investigate the integrity of the striatal dopaminergic system and cortical neural systems involved in motoric and strategic/working memory operations in healthy aging (HA) participants, patients with PD, and healthy young participants (YNC). Due to delays in obtaining approval from the Human Subjects Research Review Board of Regulatory Compliance and Quality at the USAMRMC (delayed until 2002), we were unable to obtain the radioligand for SPECT imaging. Access to a new radioligand was attempted through Boston Life Sciences, but production of that ligand was suspended. Parallel to our attempts to obtain HSRRB approval and the appropriate radioligand, we developed a novel imaging technique that probes the integrity of white matter connectivity in the human brain. We were able to combine this imaging modality with fMRI studies of aging and behavior to assess the relationship between white matter integrity and cognitive processes involved in working memory in aging and in patients with Parkinson's disease.

15. SUBJECT TERMS- nothing listed

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	24	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

Introduction

Parkinsonism is the result of decreased striatal dopamine integrity. Neurotoxins often selectively affect dopamineproducing cells and lead to behavioral manifestations of parkinsonism. The effects of parkinsonism is impaired motoric and strategic/working memory cognitive performance. Both motoric and strategic/working memory deficits also increase in community dwelling healthy elderly individuals as age increases, suggesting a link between age-associated parkinsonism and age-associated motoric and cognitive changes. In the present study we sought to investigate the integrity of the striatal dopaminergic system and cortical neural systems involved in motoric and strategic/working memory operations in healthy aging (HA) participants, patients with PD, and healthy young participants (YNC) Striatal dopaminergic integrity was to be assessed using a D_2 transporter marker ([^{123}I]-Altropane) in single photon computed tomography (SPECT) scan and cortical neural system integrity for motoric and strategic/working memory was to be assessed using functional magnetic resonance imaging (fMRI). Due to delays in obtaining approval from the Human Subjects Research Review Board of Regulatory Compliance and Quality at the USAMRMC (delayed until 2002), we were unable to obtain the radioligand for SPECT imaging. Access to a new radioligand was attempted through Boston Life Sciences, but production of that ligand was suspended. Parallel to our attempts to obtain HSRRB approval and the appropriate radioligand, we developed novel imaging techniques that probe the integrity of white matter connectivity in the human brain. We were able to combine this imaging modality with fMRI studies of aging and behavior to assess the relationship between white matter integrity and cognitive processes involved in working memory in aging and in patients with Parkinson's disease. The development of this new technique and integration with functional and structural magnetic resonance imaging allowed for its application to other disease states include Alzheimer's disease, stroke, HIV and multiple sclerosis.

Body

Impairments of cognitive ability in patients with Parkinson's disease (PD) range from mild decrements in processing speed and other "executive" functions, thought to be due to disruption of fronto-striatal function, to frank dementia, thought to be due to disruption of temporal lobe function. Despite this significant non-motor complication to PD, our understanding of the neuroanatomic substrates of the range of cognitive impairments in PD is limited. Functional neuroimaging studies have supported the notion of separable neural systems that underlie cognitive functions. The overall goal of this project was to use advance neuroimaging techniques to investigate the integrity of the striatal dopaminergic system and cortical neural systems involved in motoric and strategic/working memory operations in healthy aging (HA) participants, patients with PD, and healthy young participants (YNC). To this end, we have developed and integrated novel imaging techniques, including functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI) and structural MRI to study the integrity the frontostriatal system in patients with PD compared to controls. These studies have focused on fMRI of cognitive function in patients with PD, including the adverse development of hallucinations in cognitively impaired patients with PD; the involvement of white matter pathway dysfunction in patients with PD during cognitive function and as a results of hallucinations; and the expanded use of these technical developments in other disease states including Alzheimer's disease, stroke and multiple sclerosis.

Neural functional changes associate with cognitive processing speed in normal aging and PD and hallucinations in non-demented PD

Normal aging is associated with a decrease in cognitive efficiency, as measured by processing speed, yet few studies have examined the neural correlates of this slowing of speed. The present study used functional MRI (fMRI) during performance of the Symbol Digit Modalities Test (SDMT) to examine fMRI activation differences in 15 older adults and 21 younger adults. During scanning, each participant was asked to determine whether or not a single symbol-digit pair matched one of the symbol-digit pairs from an answer key. We found that both older and younger adults co-activated a similar network of brain regions including occipital, parietal, frontal, and temporal cortices, as well as basal ganglia regions including striatum (caudate/putamen) and globus pallidus. In contrast, older adults displayed increased fMRI activation compared to younger adults in left middle frontal cortex (BA 10), left thalamus, and right precuneus (BA 19). We did not observe any brain regions where younger adults displayed greater fMRI activation than the older adults. In addition, reaction times correlated with fMRI activation to a greater extent in older adults

than in younger adults. These data support the notion that slower processing speed in older adults is associated with altered functional activity in fronto-striatal regions critical for normal SDMT performance.

We extended these finding in a study of fMRI indices of functional integrity in a sample of 24 non-demented PD subjects and 20 matched control subjects. We were interested in the functional correlates to cognitive processing speed, a domain often impaired in early PD. The subjects underwent fMRI scanning while completing a cognitive processing speed task, the Symbol Digits Modality Test, in the magnet. Post processing of fMRI scans allowed us to control for the effects of movement, including gross body movement and tremor. Comparison between PD and control subjects was conducted using the general linear model module using a fMRI analysis program, Statistical Parametric Mapping (Wellcome Department of Cognitive Neurology, London, UK) with a conservative statistical threshold (False Discovery Rate = .05). Our results were quite compelling in demonstrating abnormal fronto-striatal function. Figure 1 presents the results of this study. Although speed and accuracy of performance was not significantly different between the groups, there was a significant decrease in fMRI activation in the PD sample in the right frontal lobe, caudate nucleus, thalamus and cingulate gyrus. There were no regions of increased fMRI activation in the PD compared to control sample. These finding led to the conclusion that fronto-striatal activation are decreased in non-demented PD patients during a processing speed task in comparison to age-matched controls. The relationship of this decrease to structural markers is not known, nor is the extent of the decrease in PD patients with MCI-O, MCI-M or PDD. These results have been published and presented in different venues (Stebbins, Carrillo, Gabrieli, 2001; Carrillo et al., 2001; Carrillo et al., 2002; Stebbins et al., 2002; Stebbins et al., 2006).

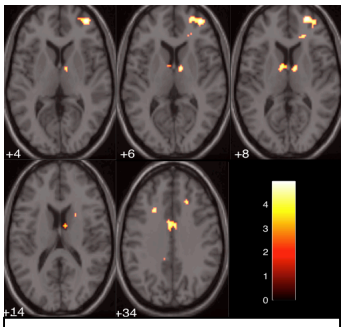

Figure 1. Decreased fMRI activation in PD during processing speed task

Visual hallucinations are a frequent and chronic condition among patients with PD and are associated with decreased cognitive function. The occurrence of hallucinations in this population leads to increased morbidity, nursing home placement and related mortality. Very little research has focused on the neuroanatomical changes related to this disabling and progressive complication of chronically treated PD, and we applied our fMRI and DTI developments to visual hallucinations in patients with PD. We examined the differences in cortical activation in hallucinating and non-hallucinating PD patients to primary (stroboscobic) and kinematic visual stimulation. These two visual stimulation conditions were chosen to assess basic visual processing (stroboscopic) as well as movement related perception (kinematic) because visual hallucinations in PD have a stereotypic

presentation that includes motion. We matched 12 hallucinating PD patients to 12 non-hallucinating patients for gender, age, duration of PD, dopaminergic drug exposure, and Hoehn and Yahr stage. Both hallucinating and non-hallucinating PD patients demonstrated activation of primary visual cortex during stroboscopic stimulation, but the hallucinating patients had diminished activation in this region (Figure 2). During kinematic stimulation, non-hallucinators demonstrated robust activation in area V5/MT, a region associated with the perception of motion. The hallucinators, however, did not show any super-threshold activation in this region. Rather, hallucinators demonstrated activation in the superior frontal lobe. These results demonstrate an aberration in processing of visual stimuli in PD patients with hallucinations compared to matched non-hallucinating PD patients. Specifically, primary visual processing results in diminished primary visual cortex activation and kinematic stimulation results in an absence of V5/MT activation with an increase in frontal activation in the hallucinators. DTI results of these same patients revealed decreased white matter integrity (decreased fractional anisotropy (FA)) in the regions of the optic radiations and the frontal forceps. These results have been published and presented in different venues (Stebbins et al., 2004; Goetz et al., 2002; Goetz, Carrillo et al., 2002; Stebbins, 2005).

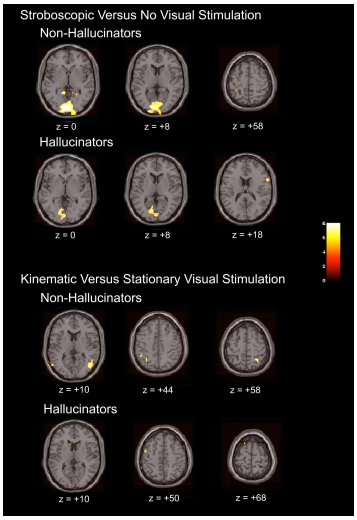

Figure 2. fMRI activation during stroboscopic (upper panel) and kinematic (lower panel)

Diffusion tensor imaging examination of white matter integrity change in PD: A major part of our effort in this project has been the integration of multimodal imaging. One technique that we have developed is the use of diffusion tensor imaging and its combination with other neuroimaging modalities. To this end, we examined changes in white matter integrity in non-demented patients with PD compared to controls, using diffusion tensor imaging (DTI). DTI provides a measure of the microstructural integrity of tissue by measuring the organization of hydrogen diffusion. We enrolled 15 PD patients and 15 age matched controls who underwent DTI scanning. The processing of these images allows us to measure white matter integrity through the metric fractional anisotropy; the directional organization of diffusion. We found regions of decreased white matter integrity in the PD sample compared to controls in frontal forceps, internal capsule, and superior thalamic peduncle (Figure 3). There were no

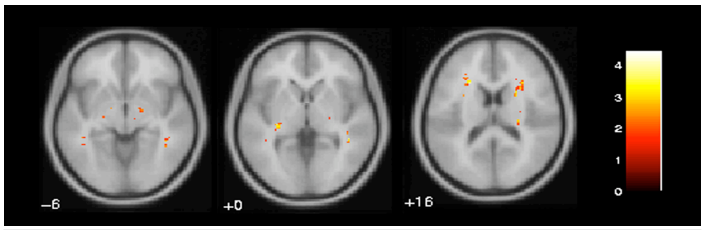

Figure 3. Regions of decreased white matter integrity in PD compared to NC (fractional anisotropy:FA).

regions of decreased white matter integrity in the controls compared to PD sample. The measure of white matter integrity, fractional anisotropy, significantly correlated with measures of cognitive speed behavioral performance ($r = .73$, $p < .001$). These results demonstrate underlying white matter changes in PD that are associated with cognitive performance. When considering the relationship of cognition to neural structures and functioning, it will be important to consider the role of white matter and have been published and present in various venues (Stebbins, Poldrack et al., 2001; Stebbins, Carrillo et al., 2001; Stebbins, Carrillo, Moseley et al., 2002; Stebbins, Carrillo, Goetz et al,. 2002; Stebbins, Carrillo, Rypma et al., 2002; Stein et al., 2005; Stebbins 2009).

Key Research Accomplishments:

- Disruption of frontostriatal function during processing speed task in PD compared to control.

- Correlation of fMRI measures of frontostriatal function to behavioral measures of executive function in PD/

- Disruption of "typical" occipital processing of visual information in PD with hallucination. Over activation of frontal regions during visual processing in PD with hallucinations.

- Disruption of frontostriatal white matter pathways in PD compared to controls.

- Inverse correlation between white matter integrity measures and behavioral measures of executive function in PD.

- Development of fMRI probes of executive function with specific emphasis on cognitive efficiency and cognitive processing speed.

- Development of diffusion tensor imaging (DTI) MRI protocols for the assessment of white matter integrity.

- Technical development of multimodal image registration and normalization for use in PD populations

- Technical development of DTI tractographic methods for co-registration with fMRI and structural MRI images.

Reportable Outcomes:

Manuscripts, abstracts, presentations:

Carrillo, M.C., Rypma, B., Gabrieli, J.D.E., Bennett, D.A., Wilson, R.S., Stebbins, G.T. Neural activity and processing speed in young and old: fMRI activity performance of the Digit Symbol Substitution Test. ProgramNo. 277.8. 2002 Abstract Viewer/Itinerary Planner, Washington, DC: Society for Neuroscience, 2002. CD-ROM.

Carrillo, M.C., Rypma, B., Gabrieli, J.D.E., Goetz, C.G., Stebbins, G.T. (2001). Neural activity and processing speed in Parkinson's disease: fMRI activity during performance of the Digit-Symbol Substitution Test. Society for Neurosciences Abstracts, 27, 311.14.

Cox, J.L., Glisky, E.L., Stebbins. G.T., Ryan, L. Dissociation of neural substrates supporting executive function and memory in normal aging: a VBM study. Program No. 127.2 2005 Abstract Viewer/Itinerary Planner. Washington, DC.: Society for Neuroscience.

Goetz, C.G., Carrillo, M.C., Medina, D., Gabrieli, J.D.E., Stebbins, G.T. (2002). fMRI activation in Parkinson's disease patients with hallucinations. Neurology, 58 (Suppl 3), A201.

Goetz, C.G., Moseley, M.E., Carrillo, M.C., Gabrieli, J.D., Stebbins, G.T. (2002).White matter microstructural integrity in Parkinsonian hallucinations: a diffusion tensor imaging study. Movement Disorders, 17(Suppl.5), S181.

Medina, D., deToledo-Morrell, L., Urresta, F., Gabrieli, J.D.E., Moseley, M.E., Flesichman, D.A., Bennett, D.A., Leurgans, S., Turner, D.A., Stebbins, G.T.. White matter changes in mild cognitive impairment and AD: a diffusion tensor imaging study. Neurobiol Aging 2006;27:663-672.

Medina, D.A., Stebbins, G.T., deToledo-Morrell, L., Gabrieli, J.D.E., Moseley, M., Bammer, R., Bennett, D.A. DTI detects dissociated patterns on regional distribution of white matter changes in the elderly. Program No. 542.13 2005 Abstract Viewer/Itinerary Planner. Washington, DC.: Society for Neuroscience.

Murphy CM, Trivedi MA, Shah R, Gabrieli JDE, Gabrieli SW, Stebbins GT. fMRI activation differences between intentional and incidental encoding schemes in the medial temporal lobes for normal individuals and those with amnestic mild cognitive impairment. Program No. 831. Neuroscience 2008 Abstracts. San Diego, CA: Society for Neuroscience, 2009. Online

Murphy, C.M., Pagonabarraga, J., Trivedi, M.A., Shah, R.C., Gabrieli, J.D.E., Stebbins, G.T. The effects of spatial normalization and white mater probability masking on diffusion tensor imaging data. Program No 668.6. 2007 Neuroscience Meeting Planner. San Diego, CA:

Society for Neuroscience, 2007, CD-ROM .

Nyenhuis, D., Stebbins, G., Wang, C., Freels, S., Shah, N., Johnson, J., deToledo-Morrell, L., Sripathirathan, K., Bammer, R., Moseley, M., Gorelick, P.. Correlations between fractional anisotropy and cognitive function in ischemic stroke are influenced by white matter classification probabilities. Paper presented at the 2nd annual meeting of The International Society for Vascular Behavioral and Cognitive Disorders (VAS-COG), Florence, Italy, 2005.

Nyenhuis' D.L., Stebbins, G.T., Wang, C., Freels, S., N Shah, N., Johnson, J., deToledo-Morrell, L., Sripathirathan, K., Bammer, R., Moseley, M., Gorelick, P.B. (2005). The influence of white matter classification probability on the relation of fractional anisotropy and cognitive function in ischemic stroke. International Society of Magnetic Resonance in Medicine. Lake Louise, Canada.

Pedelty, L., Nyenhuis, D., Stebbins, G., Gencheva, E., deToledo-Morrell, L., Berry-Kravis, E., Freels, S., Sripathirathan, K., Wang, C., Byrd, S., Jhaveri, M., Gorelick, P.. Risk markers for vascular cognitive impairment – no dementia (vcind) and vascular dementia (vad) after stroke. Paper presented at the 2nd annual meeting of The International Society for Vascular Behavioral and Cognitive Disorders (VAS-COG), Florence, Italy, 2005.

Rogalski EJ, Murphy CM, deToledo-Morrell L, Barnes CA, Shah RC, Stebbins GT. Parahippocampal white matter integrity as function of healthy elderly individuals and in amnestic mild cognitive impairment. Program No. 47. Neuroscience 2008 Abstracts. San Diego, CA: Society for Neuroscience, 2009. Online.

Rogalski EJ, Murphy CM, deToledo-Morrell L, Shah RC, Moseley ME, Bammer R, Stebbins GT. Changes in parahippocampal white matter integrity in amnestic mild cognitive impairment: a diffusion tensor imaging study. Behavioural Neurology 2009;21:51-61.

Rossi MA, Stebbins GT, Murphy C, Greene D, Brinker S, Sarcu D, Tenharmsel A, Stoub T, Stein MA, Hoeppner TJ, Byrne RW, Moseley ME, Bammer RA, Bild S, Dennis J, Arnett N, Balabanov A, Bergen D, Kanner AM, Smith MC. Predicting white matter targets for direct neurostimulation therapy. Epilepsy Research 2010;PMID:20728313.

Shukla D, Kaiser CC, Stebbins GT, Feinstein DL. Effects of pioglitazone on diffusion tensor imaging indices in multiple sclerosis patients. Neuroscience Letters 2010; Epub PMID 20144689.

Simon, T.J., Wu, Z., Avants, B., Zhang, H., Gee, J.C., Stebbins, G.T.. Atypical cortical connectivity and visuospatial cognitive impairments are related in children with chromosome 22q11.2 deletion syndrome. Behavior and Brain Function, 2008;4:25.

Simon, T.J., Wu, Z., Stebbins, G.T. Frontoparietal hypoconnectibity

might explain cognitive dysfunction in children with chromosome 22q 11.2 deletion syndrome. Program No 695.8. 2007 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience, 2007, CD-ROM.

Smith CA, Stebbins GT, Bartt RE, Kessler HA, Adeyemi OM, Martin E, Bammer R, Moseley ME. Gender effects on HIV-associated white matter alterations: a voxel-wise DTI study. Brain Imaging and Behavior 2008;2:117-191.

Smith, C.A., Stebbins, G.T., Bartt, R., Kessler, H., Bammer, R., Moseley, M. Altered white matter integrity in older adults with HIV. NeuroImage 2007;36(Suppl 1):S110.

Smith, C.A., Stebbins, G.T., Bartt, R.E., Kessler, H., Bammer, R., Moseley, M. (2005). Effects of HIV-1 infection and aging on normal appearing white matter integrity. International Society of Magnetic Resonance in Medicine. Lake Louise, Canada.

Smith, C.A., Stebbins, G.T., Bartt, R.E., Kessler, H.A., Adeyemi, O.M., Martin, E., Bammer, R., Moseley, M.E.. White matter anisotropy and depression symptoms in patients with HIV. Journal of Neuropsychiatry and Clinical Neurosciences 2008;20:458-465.

Stebbins GT, Murphy CM. Diffusion tensor imaging in Alzheimer's disease and mild cognitive impairment. Behavioural Neurology 2009;21:39-49..

Stebbins GT. (2009). Diffusion tensor imaging in Parkinson's disease. In K. Kompoliti, L. Verhagen, C. Comella, C. Goetz, J. Goldman, J. Kordower, & K. Shannon (Eds.), Encyclopedia of movement disorders. Oxford, England: Elsevier Ltd.

Stebbins, G. T., Carrillo, M. C., Gabrieli, J. D. E. (2001). Functional neuroimaging and behavioral analysis of cognitive changes in Parkinson's disease. Symposium presented at the annual meeting of the American Psychiatric Association, New Orleans, LA, May.

Stebbins, G. T., Poldrack, R. A., Klingberg, T., Carrillo, M. C., Desmond, J. E., Moseley, M. E., Hedehus, M., Wilson, R. S., Karni, O., Bennett, D. A., deToledo-Morrell, L., Gabrieli, J. D. E. (2001). Aging effects on white matter integrity and processing speed: a diffusion tensor imaging study. Neurology, 56 (Suppl 3), A374.

Stebbins, G.T., Bernard, B.A., Fan, W., Leurgans, S.E., Goetz, C.G. Cognitive functioning and hallucinations in Parkinson's disease. Ann Neurol 2005;58:S56.

Stebbins, G.T., Berry-Kravis, E., Nyenhuis, D.L., Freels, S., Johnson, J., Wang, C., deToledo-Morrell, L., Sripathirathan, K., Bammer, R., Moseley, M., Gabrieli, J.D.E., Gorelick, P.B. (2005). Interaction of longitudinal changes in fractional anisotropy and Apo E status in ischemic stroke patients. International Society of Magnetic Resonance in Medicine. Lake Louise, Canada.

Stebbins, G.T., Berry-Kravis, E., Nyenhuis, D.L., Wang, C., deToledo-Morrell, L., Gencheva, E., Bammer, R., Moseley, M., Gabrieli, J.D.E., Gorelick, P.B.. Apoe 4 associated decline in white matter integrity in ischemic stroke. Paper presented at the 2nd annual meeting of The International Society for Vascular Behavioral and Cognitive Disorders (VAS-COG), Florence, Italy, 2005.

Stebbins, G.T., Carrillo, M.C., Bangen, K.J., Moseley, M.E., Katsamakis, G., Stefoski, D., Turner, D.A., Gabrieli, J.D.E. (2003). Relationship of white matter integrity in multiple sclerosis with executive and non-executive cognitive functions: a DTI study. Program No. 213.7 2003 Abstract Viewer/Itinerary Planner. Washington, DC.: Society for Neuroscience.

Stebbins, G.T., Carrillo, M.C., Goetz, C.G., Moseley, M.E., Gabrieli, J.D. (2002). Dissociation of frontal and prefrontal white matter integrity to cognitive and motor behaviors in Parkinson's disease: a diffusion tensor imaging study. Movement Disorders, 17 (Suppl. 5), S172.

Stebbins, G.T., Carrillo, M.C., Medina, D., deToledo-Morrell, L., Klingberg, T., Poldrack, R.A., Moseley, M.E., Karni, O., Wilson, R.S., Bennett, D.A., Gabrieli, J.D.E. (2001). Frontal white matter integrity in aging and its relationship to reasoning performance: a diffusion tensor imaging study. Society for Neuroscience Abstracts, 27, 456.3.

Stebbins, G.T., Carrillo, M.C., Moseley, M.E., Wilson, R.S., Bennett, D.A., Goetz, C.G., Gabrieli, J.D.E. (2002). Microstructural integrity of normal appearing white matter in Parkinson's disease: a diffusion tensor imaging study with behavioral correlates. Neurology, 58 (Suppl 3), A200.

Stebbins, G.T., Carrillo, M.C., Rypma, B., Moseley, M.E., Goetz, C.G., Wilson, R.S., Bennett, D.A., Turner, D.A., Gabrieli, J.D.E. Cortical and subcortical contributions to processing speed in Parkinson's disease: a combined fMRI and diffusion tensor imaging study. Program No. 714.11. 2002 Abstract Viewer/Itinerary Planner, Washington, DC: Society for Neuroscience, 2002. CD-ROM.

Stebbins, G.T., Cox, J.L., Rypma, B., Gabrieli, J.D.E., Goetz, C.G. Neural substrates of cognitive efficiency in PD. Movement Disorders 2006;21(Suppl 15):S663.

Stebbins, G.T., Goetz, C.G., Carrillo, M.C., Bangen, K.J., Turner D.A., Gabrieli, J.D.E. Altered cortical visual system processing in Parkinson's disease with hallucinations: a functional MRI study. Neurology 2004;63:1409-1416.

Stebbins, G.T., Nyenhuis, D.L., Cox, J.L., deToledo-Morrell, L., Shah, N., Goetz, C., Gabrieli, J.D.E., Gorelick, P.B. Decreased white matter density in ischemic stroke patients with cognitive impairment

— no dementia: a VBM study. Program No. 410.6 2005 Abstract Viewer/Itinerary Planner. Washington, DC.: Society for Neuroscience.

Stebbins, G.T., Nyenhuis, D.L., Freels, S., deToledo-Morrell, L., Gencheva, E., Moseley, M.E., Bangen, K.J., Turner, D.A., Gabrieli, J.D.E., Gorelick, P.B.. Application of Diffusion Tensor Imaging in Vascular Dementia and Vascular Cognitive Impairment. J Neurol Sci 2004;226:147.

Stebbins, G.T., Nyenhuis, D.L., Freels, S., deToledo-Morrell, L., Gencheva, E., Moseley, M.E., Bangen, K.J., Turner, D.A., Gabrieli, J.D.E., Gorelick, P.B.. A diffusion tensor imaging study of normal appearing white matter integrity in recent ischemic stroke - relationship to cognitive function. J Neurol Sci 2004;226:147.

Stebbins, G.T., Smith, C.A., Bartt, R., Kessler, H.A., Martin, E., Bammer, R., Moseley, M. HIV-associated regional decrease in normal appearing white matter integrity: a diffusion tensor imaging study. Ann Neurol 2005;58:S62.

Stebbins, G.T., Smith, C.A., Bartt, R.E., Kessler, H.A., Adeyemi, O.M., Martin, E., Cox, J.L., Bammer, R., Moseley, M.. HIV-associated alterations in normal appearing white matter: a voxel-wise DTI study. Journal of Acquired Immune Deficiency Syndromes, 2007;46:564-573.

Stein, M.A., Stebbins, G.T., Wuu, J., Leurgans, S.E., Bammer, R. Fractional anisotropy as a measure of white matter integrity and its relationship to psychomotor processing speed in normal aging. Ann Neurol 2005;58:S50.

Urresta, F., Medina, D., deToledo-Morrell, L., Gabrieli, J.D.E., Klingberg, T., Moseley, M.E., Wilson, R.S., Bennett, D.A., Stebbins, G.T. (2001). In vivo detection of white matter changes in Alzheimer's disease with diffusion tensor imaging. Society for Neuroscience Abstracts, 27, 426.1.

Wang C, Stebbins GT, Median DA, Shah RC, Bammer R, Moseley ME, deToledo-Morrell L. Atrophy and dysfunction of parahippocampal white matter in mild Alzheimer’s disease. Neurobiology of Aging 2010; Epub PMID 20359781.

Wang, C., deToldeo-Morrell, L., Nyenhuis, D., Gencheva, E., Gorelick, P., Turner, D., Moseley, M., Stebbins, G.T.. Longitudinal diffusion tensor imaging study of the microstructural integrity of white matter in ischemic stroke patients. J Neurol Sci 2004;226:153.

Wang, C., deToledo-Morrell, L., Nyuenhuis, D., Freels, S., Gencheva, E., Moseley, M.E., Turner, D.A., Gabrieli, J.D.E., Gorelick, P.D., Stebbins, G.T. (2003). Longitudinal changes in anisotropic diffusion in ischemic stroke: relationship to initial motor impairment. Program No. 620.13 2003 Abstract Viewer/Itinerary Planner. Washington, DC.: Society for Neuroscience.

Wang, C., Stebbins, G.T., Nyenhuis, D.L., deToledo-Morrell, L., Freels, S., Gencheva, E., Pedelty, L., Sripathirathan, K., Moseley, M., Turner, D.A., Gabrieli, J.D.E., Gorelick, P.B.. Longitudinal changes in white matter following ischemic stroke: a three-year follow-up study. Neurobiol Aging, 2006;27:1827-1833.

Willamson J, Nyenhuis D, Stebbins GT, Lamb D, Simkus V, Sripathirathan K, Wang C. deToledo-Morrell L, Gorelick P. Regional differences in relationships between apparent white matter integrity, cognition and mood in patients with ischemic stroke. Journal of Clinical and Experimental Neuropsychology 2010; Epub PMID 20155558.

Patents and licenses applied for and/or issued:

None

Degrees obtained that are supported by this award:

None

Development of cell lines, tissue or serum repositories:

None

Infomatics such as databases and animal models, etc.:

None

Funding applied for based on work supported by this award:

Agency: National Institute of Neurological Disorders and Stroke (N057514)

Dates of award: 2007 - 2011

Title: Validation of the NINDS VCI Neuropsychological Protocol

Role: Site Principal Investigator

Agency: American Cancer Society (PSB06-08)

Dates of award: 2007 - 2010

Title: Non-Hodgkin's Lymphoma without CNS Involvement: Effects of Treatment in an Older Sample

Role: Co-Investigator.

Agency: National Institute on Aging (AG023491)

Dates of award: 2003 - 2007

Title: Microstructural brain white matter in aging and HIV

Role: Co-Investigator.

Agency: Rayman Family Multiple Sclerosis Award

Dates of award: 2000 - 2007

Title: Advanced Neuroimaging and Behavioral Analysis of Cognitive Changes in Multiple Sclerosis

Role: Principal Investigator.

Employment or research opportunities applied for and/or received based on experience/training supported by this award:

None

Conclusions:

There are multiple non-motor complications found in PD including cognitive impairments. These impairments include deficits in functions such as executive abilities, working memory and processing speed. Our project was designed to investigate the neurological substrates that support these functions and study the effect of PD on such substrates. We found that functional MRI indices correlated with executive processes in young controls, aged controls and patients with PD. These correlations all identified the frontostriatal neural systems as pivotal to the cognitive processes involved in processing speed and efficiency. Spanning across the life span in healthy individuals we found increases in the fMRI markers of functional status. This same increase in frontostriatal activation was noted in non-demented patients with PD. These results suggest that in the aging system, and in the PD system, increased frontostriatal activity is required during the execution of processing speed tasks. In a separate study, we found that the typical pattern of occipital activation during visual stimulation was disrupted in PD patient with visual hallucinations. Visual hallucinations are a common cognitive problem experienced by patients with PD, particularly late in the course of their disease. The alteration we found in hallucinating PD patients was a decrease in occipital activation and an increase in frontal lobe activation. We interpreted these finding as indicative of and reversal of the typical bottom-up processing of visual information to a top-down processing model. In addition to these functional imaging studies, we developed the application of diffusion tensor imaging to examine the contribution of white matter integrity loss to cognitive functional decreases in PD. We found that there were location-specific losses of white matter integrity in the frontostriatal system, include the outflow regions from the frontal lobes and the striatum. Additionally we found that white matter integrity was decreased in the visual system in PD patients with hallucinations. The technological developments of this application included the coregistration of fMRI imaging, structural MRI imaging and DTI imaging. In addition, we had to account for varying amounts of head movement across the different imaging modalities. These developments have allowed us to apply multimodal imaging to other diseases of the aged, include healthy aging, mild cognitive impairment and Alzheimer's disease as well as other disease states such as multiple sclerosis, cancer and HIV. These studies have led to a greater understanding the underlying neural substrates supporting cognitive function in PD and other diseases. This knowledge not only moves the field forward in understanding of system integration, but also may provide markers for the development and application of treatments.

References:

Carrillo, M.C., Rypma, B., Gabrieli, J.D.E., Bennett, D.A., Wilson, R.S., Stebbins, G.T. Neural activity and processing speed in young and old: fMRI activity performance of the Digit Symbol Substitution Test. ProgramNo. 277.8. 2002 Abstract Viewer/Itinerary Planner, Washington, DC: Society for Neuroscience, 2002. CD-ROM.

Carrillo, M.C., Rypma, B., Gabrieli, J.D.E., Goetz, C.G., Stebbins, G.T. (2001). Neural activity and processing speed in Parkinson's disease: fMRI activity during performance of the Digit-Symbol Substitution Test. Society for Neurosciences Abstracts, 27, 311.14.

Cox, J.L., Glisky, E.L., Stebbins. G.T., Ryan, L. Dissociation of neural substrates supporting executive function and memory in normal aging: a VBM study. Program No. 127.2 2005 Abstract Viewer/Itinerary Planner. Washington, DC.: Society for Neuroscience.

Goetz, C.G., Carrillo, M.C., Medina, D., Gabrieli, J.D.E., Stebbins, G.T. (2002). fMRI activation in Parkinson's disease patients with hallucinations. Neurology, 58 (Suppl 3), A201.

Goetz, C.G., Moseley, M.E., Carrillo, M.C., Gabrieli, J.D., Stebbins, G.T. (2002).White matter microstructural integrity in Parkinsonian hallucinations: a diffusion tensor imaging study. Movement Disorders, 17(Suppl.5), S181.

Medina, D., deToledo-Morrell, L., Urresta, F., Gabrieli, J.D.E., Moseley, M.E., Flesichman, D.A., Bennett, D.A., Leurgans, S., Turner, D.A., Stebbins, G.T.. White matter changes in mild cognitive impairment and AD: a diffusion tensor imaging study. Neurobiol Aging 2006;27:663-672.

Medina, D.A., Stebbins, G.T., deToledo-Morrell, L., Gabrieli, J.D.E., Moseley, M., Bammer, R., Bennett, D.A. DTI detects dissociated patterns on regional distribution of white matter changes in the elderly. Program No. 542.13 2005 Abstract Viewer/Itinerary Planner. Washington, DC.: Society for Neuroscience.

Murphy CM, Trivedi MA, Shah R, Gabrieli JDE, Gabrieli SW, Stebbins GT. fMRI activation differences between intentional and incidental encoding schemes in the medial temporal lobes for normal individuals and those with amnestic mild cognitive impairment. Program No. 831. Neuroscience 2008 Abstracts. San Diego, CA: Society for Neuroscience, 2009. Online

Murphy, C.M., Pagonabarraga, J., Trivedi, M.A., Shah, R.C., Gabrieli, J.D.E., Stebbins, G.T. The effects of spatial normalization and white mater probability masking on diffusion tensor imaging data. Program No 668.6. 2007 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience, 2007, CD-ROM .

Nyenhuis, D., Stebbins, G., Wang, C., Freels, S., Shah, N., Johnson, J., deToledo-Morrell, L., Sripathirathan, K., Bammer, R., Moseley, M., Gorelick, P.. Correlations between fractional anisotropy and cognitive function in ischemic stroke are influenced by white matter classification probabilities. Paper presented at the 2nd annual meeting of The International Society for Vascular Behavioral and Cognitive Disorders (VAS-COG), Florence, Italy, 2005.

Nyenhuis' D.L., Stebbins, G.T., Wang, C., Freels, S., N Shah, N., Johnson, J., deToledo-Morrell, L., Sripathirathan, K., Bammer, R., Moseley, M., Gorelick, P.B. (2005). The influence of white matter classification probability on the relation of fractional anisotropy and cognitive function in ischemic stroke. International Society of Magnetic Resonance in Medicine. Lake Louise, Canada.

Pedelty, L., Nyenhuis, D., Stebbins, G., Gencheva, E., deToledo-Morrell, L., Berry-Kravis, E., Freels, S., Sripathirathan, K., Wang, C., Byrd, S., Jhaveri, M., Gorelick, P.. Risk markers for vascular cognitive impairment – no dementia (vcind) and vascular dementia (vad) after stroke. Paper presented at the 2nd annual meeting of The International Society for Vascular Behavioral and Cognitive Disorders (VAS-COG), Florence, Italy, 2005.

Rogalski EJ, Murphy CM, deToledo-Morrell L, Barnes CA, Shah RC, Stebbins GT. Parahippocampal white matter integrity as function of healthy elderly individuals and in amnestic mild cognitive impairment. Program No. 47. Neuroscience 2008 Abstracts. San Diego, CA: Society for Neuroscience, 2009. Online.

Rogalski EJ, Murphy CM, deToledo-Morrell L, Shah RC, Moseley ME, Bammer R, Stebbins GT. Changes in parahippocampal white matter integrity in amnestic mild cognitive impairment: a diffusion tensor imaging study. Behavioural Neurology 2009;21:51-61.

Rossi MA, Stebbins GT, Murphy C, Greene D, Brinker S, Sarcu D, Tenharmsel A, Stoub T, Stein MA, Hoeppner TJ, Byrne RW, Moseley ME, Bammer RA, Bild S, Dennis J, Arnett N, Balabanov A, Bergen D, Kanner AM, Smith MC. Predicting white matter targets for direct neurostimulation therapy. Epilepsy Research 2010;PMID:20728313.

Shukla D, Kaiser CC, Stebbins GT, Feinstein DL. Effects of pioglitazone on diffusion tensor imaging indices in multiple sclerosis patients. Neuroscience Letters 2010; Epub PMID 20144689.

Simon, T.J., Wu, Z., Avants, B., Zhang, H., Gee, J.C., Stebbins, G.T.. Atypical cortical connectivity and visuospatial cognitive impairments are related in children with chromosome 22q11.2 deletion syndrome. Behavior and Brain Function, 2008;4:25.

Simon, T.J., Wu, Z., Stebbins, G.T. Frontoparietal hypoconnectibity might explain cognitive dysfunction in children with chromosome 22q 11.2 deletion syndrome. Program No 695.8. 2007 Neuroscience Meeting

Planner. San Diego, CA: Society for Neuroscience, 2007, CD-ROM.

Smith CA, Stebbins GT, Bartt RE, Kessler HA, Adeyemi OM, Martin E, Bammer R, Moseley ME. Gender effects on HIV-associated white matter alterations: a voxel-wise DTI study. Brain Imaging and Behavior 2008;2:117-191.

Smith, C.A., Stebbins, G.T., Bartt, R., Kessler, H., Bammer, R., Moseley, M. Altered white matter integrity in older adults with HIV. NeuroImage 2007;36(Suppl 1):S110.

Smith, C.A., Stebbins, G.T., Bartt, R.E., Kessler, H., Bammer, R., Moseley, M. (2005). Effects of HIV-1 infection and aging on normal appearing white matter integrity. International Society of Magnetic Resonance in Medicine. Lake Louise, Canada.

Smith, C.A., Stebbins, G.T., Bartt, R.E., Kessler, H.A., Adeyemi, O.M., Martin, E., Bammer, R., Moseley, M.E.. White matter anisotropy and depression symptoms in patients with HIV. Journal of Neuropsychiatry and Clinical Neurosciences 2008;20:458-465.

Stebbins GT, Murphy CM. Diffusion tensor imaging in Alzheimer's disease and mild cognitive impairment. Behavioural Neurology 2009;21:39-49..

Stebbins GT. (2009). Diffusion tensor imaging in Parkinson's disease. In K. Kompoliti, L. Verhagen, C. Comella, C. Goetz, J. Goldman, J. Kordower, & K. Shannon (Eds.), Encyclopedia of movement disorders. Oxford, England: Elsevier Ltd.

Stebbins, G. T., Carrillo, M. C., Gabrieli, J. D. E. (2001). Functional neuroimaging and behavioral analysis of cognitive changes in Parkinson's disease. Symposium presented at the annual meeting of the American Psychiatric Association, New Orleans, LA, May.

Stebbins, G. T., Poldrack, R. A., Klingberg, T., Carrillo, M. C., Desmond, J. E., Moseley, M. E., Hedehus, M., Wilson, R. S., Karni, O., Bennett, D. A., deToledo-Morrell, L., Gabrieli, J. D. E. (2001). Aging effects on white matter integrity and processing speed: a diffusion tensor imaging study. Neurology, 56 (Suppl 3), A374.

Stebbins, G.T., Bernard, B.A., Fan, W., Leurgans, S.E., Goetz, C.G. Cognitive functioning and hallucinations in Parkinson's disease. Ann Neurol 2005;58:S56.

Stebbins, G.T., Berry-Kravis, E., Nyenhuis, D.L., Freels, S., Johnson, J., Wang, C., deToledo-Morrell, L., Sripathirathan, K., Bammer, R., Moseley, M., Gabrieli, J.D.E., Gorelick, P.B. (2005). Interaction of longitudinal changes in fractional anisotropy and Apo E status in ischemic stroke patients. International Society of Magnetic Resonance in Medicine. Lake Louise, Canada.

Stebbins, G.T., Berry-Kravis, E., Nyenhuis, D.L., Wang, C., deToledo-Morrell, L., Gencheva, E., Bammer, R., Moseley, M., Gabrieli, J.D.E.,

Gorelick, P.B.. Apoe 4 associated decline in white matter integrity in ischemic stroke. Paper presented at the 2nd annual meeting of The International Society for Vascular Behavioral and Cognitive Disorders (VAS-COG), Florence, Italy, 2005.

Stebbins, G.T., Carrillo, M.C., Bangen, K.J., Moseley, M.E., Katsamakis, G., Stefoski, D., Turner, D.A., Gabrieli, J.D.E. (2003). Relationship of white matter integrity in multiple sclerosis with executive and non-executive cognitive functions: a DTI study. Program No. 213.7 2003 Abstract Viewer/Itinerary Planner. Washington, DC.: Society for Neuroscience.

Stebbins, G.T., Carrillo, M.C., Goetz, C.G., Moseley, M.E., Gabrieli, J.D. (2002). Dissociation of frontal and prefrontal white matter integrity to cognitive and motor behaviors in Parkinson's disease: a diffusion tensor imaging study. Movement Disorders, 17 (Suppl. 5), S172.

Stebbins, G.T., Carrillo, M.C., Medina, D., deToledo-Morrell, L., Klingberg, T., Poldrack, R.A., Moseley, M.E., Karni, O., Wilson, R.S., Bennett, D.A., Gabrieli, J.D.E. (2001). Frontal white matter integrity in aging and its relationship to reasoning performance: a diffusion tensor imaging study. Society for Neuroscience Abstracts, 27, 456.3.

Stebbins, G.T., Carrillo, M.C., Moseley, M.E., Wilson, R.S., Bennett, D.A., Goetz, C.G., Gabrieli, J.D.E. (2002). Microstructural integrity of normal appearing white matter in Parkinson's disease: a diffusion tensor imaging study with behavioral correlates. Neurology, 58 (Suppl 3), A200.

Stebbins, G.T., Carrillo, M.C., Rypma, B., Moseley, M.E., Goetz, C.G., Wilson, R.S., Bennett, D.A., Turner, D.A., Gabrieli, J.D.E. Cortical and subcortical contributions to processing speed in Parkinson's disease: a combined fMRI and diffusion tensor imaging study. Program No. 714.11. 2002 Abstract Viewer/Itinerary Planner, Washington, DC: Society for Neuroscience, 2002. CD-ROM.

Stebbins, G.T., Cox, J.L., Rypma, B., Gabrieli, J.D.E., Goetz, C.G. Neural substrates of cognitive efficiency in PD. Movement Disorders 2006;21(Suppl 15):S663.

Stebbins, G.T., Goetz, C.G., Carrillo, M.C., Bangen, K.J., Turner D.A., Gabrieli, J.D.E. Altered cortical visual system processing in Parkinson's disease with hallucinations: a functional MRI study. Neurology 2004;63:1409-1416.

Stebbins, G.T., Nyenhuis, D.L., Cox, J.L., deToledo-Morrell, L., Shah, N., Goetz, C., Gabrieli, J.D.E., Gorelick, P.B. Decreased white matter density in ischemic stroke patients with cognitive impairment – no dementia: a VBM study. Program No. 410.6 2005 Abstract Viewer/Itinerary Planner. Washington, DC.: Society for Neuroscience.

Stebbins, G.T., Nyenhuis, D.L., Freels, S., deToledo-Morrell, L., Gencheva, E., Moseley, M.E., Bangen, K.J., Turner, D.A., Gabrieli, J.D.E., Gorelick, P.B.. Application of Diffusion Tensor Imaging in Vascular Dementia and Vascular Cognitive Impairment. J Neurol Sci 2004;226:147.

Stebbins, G.T., Nyenhuis, D.L., Freels, S., deToledo-Morrell, L., Gencheva, E., Moseley, M.E., Bangen, K.J., Turner, D.A., Gabrieli, J.D.E., Gorelick, P.B.. A diffusion tensor imaging study of normal appearing white matter integrity in recent ischemic stroke - relationship to cognitive function. J Neurol Sci 2004;226:147.

Stebbins, G.T., Smith, C.A., Bartt, R., Kessler, H.A., Martin, E., Bammer, R., Moseley, M. HIV-associated regional decrease in normal appearing white matter integrity: a diffusion tensor imaging study. Ann Neurol 2005;58:S62.

Stebbins, G.T., Smith, C.A., Bartt, R.E., Kessler, H.A., Adeyemi, O.M., Martin, E., Cox, J.L., Bammer, R., Moseley, M.. HIV-associated alterations in normal appearing white matter: a voxel-wise DTI study. Journal of Acquired Immune Deficiency Syndromes, 2007;46:564-573.

Stein, M.A., Stebbins, G.T., Wuu, J., Leurgans, S.E., Bammer, R. Fractional anisotropy as a measure of white matter integrity and its relationship to psychomotor processing speed in normal aging. Ann Neurol 2005;58:S50.

Urresta, F., Medina, D., deToledo-Morrell, L., Gabrieli, J.D.E., Klingberg, T., Moseley, M.E., Wilson, R.S., Bennett, D.A., Stebbins, G.T. (2001). In vivo detection of white matter changes in Alzheimer's disease with diffusion tensor imaging. Society for Neuroscience Abstracts, 27, 426.1.

Wang C, Stebbins GT, Median DA, Shah RC, Bammer R, Moseley ME, deToledo-Morrell L. Atrophy and dysfunction of parahippocampal white matter in mild Alzheimer’s disease. Neurobiology of Aging 2010; Epub PMID 20359781.

Wang, C., deToldeo-Morrell, L., Nyenhuis, D., Gencheva, E., Gorelick, P., Turner, D., Moseley, M., Stebbins, G.T.. Longitudinal diffusion tensor imaging study of the microstructural integrity of white matter in ischemic stroke patients. J Neurol Sci 2004;226:153.

Wang, C., deToledo-Morrell, L., Nyuenhuis, D., Freels, S., Gencheva, E., Moseley, M.E., Turner, D.A., Gabrieli, J.D.E., Gorelick, P.D., Stebbins, G.T. (2003). Longitudinal changes in anisotropic diffusion in ischemic stroke: relationship to initial motor impairment. Program No. 620.13 2003 Abstract Viewer/Itinerary Planner. Washington, DC.: Society for Neuroscience.

Wang, C., Stebbins, G.T., Nyenhuis, D.L., deToledo-Morrell, L., Freels, S., Gencheva, E., Pedelty, L., Sripathirathan, K., Moseley,

M., Turner, D.A., Gabrieli, J.D.E., Gorelick, P.B.. Longitudinal changes in white matter following ischemic stroke: a three-year follow-up study. Neurobiol Aging, 2006;27:1827-1833.

Willamson J, Nyenhuis D, Stebbins GT, Lamb D, Simkus V, Sripathirathan K, Wang C. deToledo-Morrell L, Gorelick P. Regional differences in relationships between apparent white matter integrity, cognition and mood in patients with ischemic stroke. Journal of Clinical and Experimental Neuropsychology 2010; Epub PMID 20155558.

Appendix:

None