Hippocampus Function Predicts Severity of Post-Traumatic Stress Disorder

ROBERT S. ASTUR, Ph.D.,[1,2] SARAH A. ST. GERMAIN, B.S.,[1] DAVID TOLIN, Ph.D.,[3,4]
JULIAN FORD, Ph.D.,[4] DAVID RUSSELL, and MIKE STEVENS, Ph.D.[1,2]

ABSTRACT

Post-traumatic stress disorder (PTSD) is often accompanied by memory problems and abnormal brain structure, particularly within the hippocampus. We implemented a cross-species, hippocampal-dependent task—the virtual Morris Water task—to assess hippocampal function in people with PTSD and age-matched controls during functional magnetic resonance imaging (fMRI). Performance on the task was equivalent between the groups. However, when correlating fMRI-derived hippocampal activity during this task with PTSD severity, we observe a −0.84 correlation, indicating that those with reduced hippocampal activity show more severe PTSD symptoms. This correlation is not explained by differences in task performance, IQ, duration since trauma, nor time with PTSD. Hence, PTSD severity is predicted by functionally assessing the hippocampus using the virtual Morris water task, suggesting that this task may be used to identify those at risk for developing PTSD following a trauma.

INTRODUCTION

POST-TRAUMATIC STRESS DISORDER (PTSD) is a psychiatric condition that can develop after experiencing or witnessing life-threatening events such as military combat, serious accidents, terrorist attacks, rape, or personal assault. PTSD is often characterized by intrusive thoughts of the traumatic event, sleeplessness, hypersensitivity, and chronic stress. Despite these stark symptoms, PTSD is greatly under-diagnosed and has lifetime prevalence rates of approximately 13% for women and 6% for women in the US.[1] Moreover, it is estimated that 60% of men and 50% of women are exposed to a traumatic event that might potentially lead to

PTSD[2]; hence, this is an issue that is pertinent to the majority of people.

Due to the debilitating nature of symptoms, PTSD causes substantial amounts of medical illness, unemployment, and homelessness. Despite a large amount of research on PTSD, it is still unclear why some people develop PTSD, and others do not. For example, it is not overly clear how to predict which individuals might develop PTSD following a terrorist attack, a rape, or a motor vehicle accident.

Over the last decade, neuroimaging studies have revealed that certain brain structures appear abnormal in people with PTSD.[3–5] One such structure, the hippocampus, has been shown to be critical for

[1]Olin Neuropsychiatry Research Center, Institute of Living, Hartford, Connecticut.
[2]Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut.
[3]Anxiety Disorders Program, Institute of Living, Hartford, Connecticut.
[4]Department of Psychiatry, University of Connecticut School of Medicine, Farmington, Connecticut.

memory functioning[6–9] and is damaged by chronic stress.[10] Multiple MRI structural analyses have revealed reduced hippocampal volume in subjects with current, chronic PTSD,[3,5,11–18] although it is unclear how or whether these structural abnormalities translate to functional abnormalities. Research with rodents has shown that chronic stress damages the hippocampus.[10] Because of this, it has been hypothesized that these structural HPC abnormalities may be a consequence of the chronic stress that PTSD individuals undergo. However, recently, there are data that suggests that the HPC is abnormal in people *before* they experience a traumatic event that results in PTSD.[19] Hence, HPC dysfunction may be a precursor to PTSD, rather than the reverse.

Consistently, the HPC has been shown to be essential for spatial memory in numerous species, including humans.[7,20–27] Thus, to test HPC functioning in humans, we relied on an analogue of a rodent golden standard spatial memory task, the Morris water task. In this task, rodents search for a hidden escape platform in a pool of murky water. We have developed a virtual reality version of this task in humans which has demonstrated to be sensitive to HPC damage in patients with HPC excisions,[24] and the task also reliably results in HPC activity during fMRI.[25,26] These results indicate that the human HPC is both involved and necessary for spatial navigation, and this melds well with predictions from the nonhuman literature. Collectively, these results suggest that the virtual reality Morris water task can be used effectively to probe hippocampus function in people with PTSD or other psychiatric illnesses.

METHODS

Participants

Twelve patients with current PTSD were evaluated with a clinical interview (SCID) and a trauma history (TESI-AS and CAPS). PTSD patients were recruited from the local Hartford population via ads placed in local papers, and through physician referrals. Twelve healthy controls were recruited from the local population, as well as the hospital community via e-mail ads and word of mouth. Patients' diagnoses of PTSD were confirmed with the Structured Clinical Interviews for DSM IV (SCID-IV). Healthy controls were also given the SCID-IV to determine the presence of psychiatric illnesses. Healthy controls were only included if they did not have a history of substance dependence nor a lifetime history of any axis 1 disorders (excluding de-
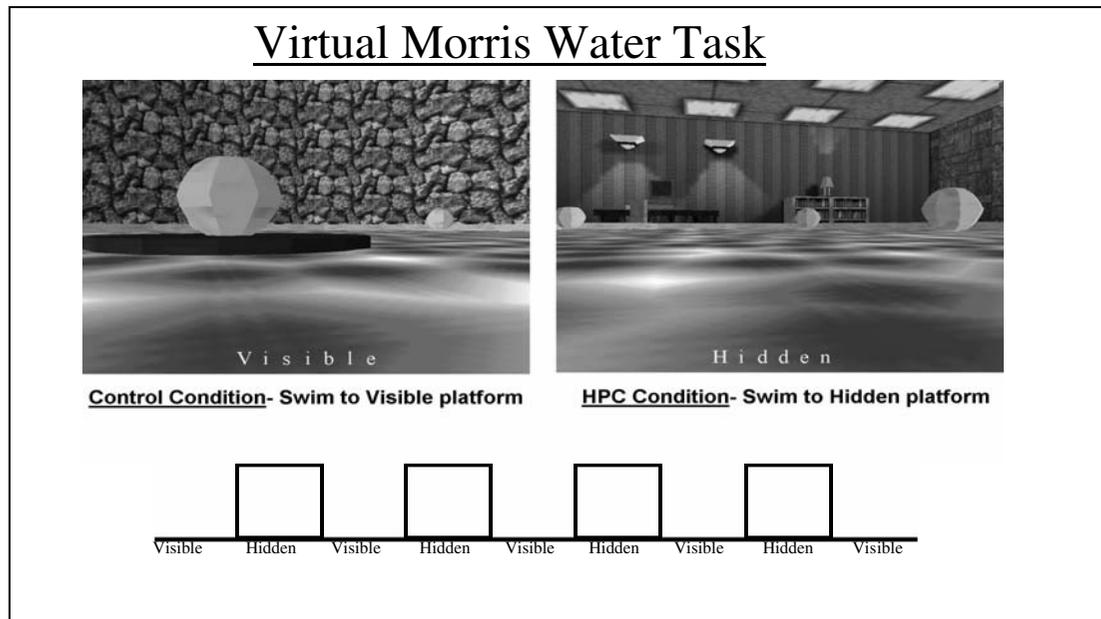

FIG. 1. Black and white screenshots of the two different test conditions during fMRI. In the Visible/Control condition, the subject can see the platform. In the Hidden/HPC condition, the platform is invisible, and the subject must use the cues in the room to remember the location of the platform. In the actual experiment, all graphics were presented in True Color.
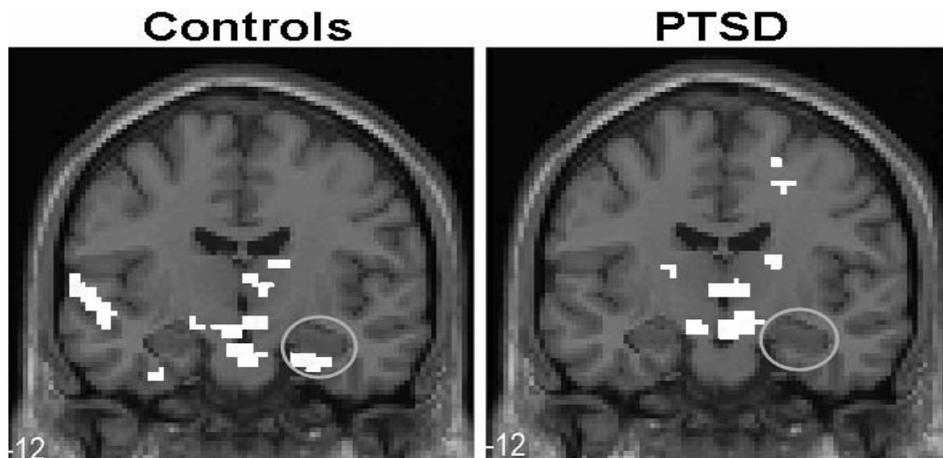
FIG. 2. Controls show more hippocampal activity (see circled area in right HPC) during the vMWT than the PTSD group.

pression). For all subjects, exclusion criteria included inability to give informed consent, a history of major head trauma, significant medical or neurological illness, and any incidental findings found by MRI scan. Healthy controls were matched to patients and relatives for age and gender. All subjects gave written informed consent after the experimental procedures had been fully explained, and all subjects were paid $20/hour to participate in the study.

CAPS

The Clinician-Administered PTSD Scale for DSM IV (CAPS)[27] is the gold standard measure to allow researchers to assess a patient's present PTSD status. The CAPS is designed to assess 25 different symptoms for PTSD, in addition to evaluating the frequency and intensity dimensions of each symptom. Four sub-scores are formed at the conclusion of the interview: intrusive re-experiencing, avoidance/numbing, hyperarousal, and an overall symptom severity index. In our study, we report correlations between HPC activity and the overall symptom severity index.

Apparatus

The virtual environment was projected via an LCD projector on a screen on the back of the MRI bore. Participants viewed the screen via a 45-degree mirror positioned over their eyes. Participants moved through the virtual environment by manipulating a MR-compatible joystick. The VR

software and analysis software were custom written by the first author.

Procedure

Participants were virtually placed in a round pool located in the center of a rectangular room. The room had a variety of textures and landmarks throughout it that made it distinct. Within the pool, there were four identical balls floating in the water. The task alternates between two conditions: a hidden condition and a visible condition. In the Hidden condition, one of the balls was floating over a hidden platform. Participants were told to use the distal cues in the room to navigate to the ball that floated above the hidden platform. The platform never moved, and stayed under the same ball for all trials. In the Visible condition, subjects navigated to a visible platform under one of the four balls. It is well established that swimming to a visible platform does not require the hippocampus. Participants were pre-trained in the both conditions outside the scanner until they were familiar with the environment, instructions, and the location of the hidden platform. Swimming to an incorrect ball resulted in a raucous buzzer noise, a small delay and slowing of movement, as if the person was swimming in quicksand.

fMRI data acquisition

Functional magnetic resonance images were collected with a Siemens Allegra 3 Tesla scanner at the Olin Neuropsychiatry Research Center. Imaging

began with the acquisition of a sagittal T2-weighted anatomic localizer scan, followed by the functional echo planar gradient echo imaging sequence prescribed perpendicular to the long axis of the hippocampus. A gradient-echo planar sequence was used to obtain T2*-weighted images (TR = 1.86 s, TE = 27 ms, Flip = 70°). Thirty-six contiguous horizontal 3-mm slices parallel to the intercommissural plane (voxel size 3.44 × 3.44 × 4 mm) were acquired sequentially. Each run was 6 min, 5 s long. There were a total of 196 images/slice acquired per run.

fMRI data analysis

Imaging data were analyzed with SPM2 (Statistical Parametric Mapping, developed by the Wellcome Institute, London, UK). Functional images were realigned/motion corrected and normalized into a standard Tailarach template. Data was then smoothed using a 8-mm isotropic Gaussian kernel and frequency filtered using a 5th-order low-pass digital Butterworth filter. The effects of the Hidden Platform phase were estimated according to the General Linear Model at each voxel. The data were modeled to a box car function convolved with the hemodynamic response function and the temporal derivative.

RESULTS

Behavioral

Behaviorally, the PTSD group and the control group were equivalent in finding the hidden and visible platforms, as evidenced by time to find the platform ($p > 0.05$). Similarly, when probing knowledge of the spatial memory of the platform by administering a no-platform probe trial during Hidden platform testing, the groups are equivalent. Specifically, controls, on average, spent 35.9% (SD = 0.21) of their "swimming" time in the correct quadrant, compared to patients' average of 33.0% (SD = 0.16).

fMRI

fMRI activation maps show that while navigating to this hidden platform, it is apparent that the control group has stronger HPC BOLD response than PTSD group (Fig. 2). See Table 1 for additional brain areas where the control group has greater brain activation responses than the PTSD group.

CAPS correlations with fMRI

PTSD severity is commonly measured by the Clinical Administered PTSD Scale.[27] We correlated severity of PTSD with HPC activity, as derived from fMRI. HPC activity predicts a subscale of the CAPS, the hyperarousal and activity scale, at −0.90, indicating that those with reduced HPC BOLD response have stronger hyperarousal and activity symptoms. Moreover, correlating HPC function with overall PTSD severity results in a −0.84 correlation (Fig. 3). However, this HPC function is not predicted by estimated WAIS (IQ), time since the trauma, duration of diagnosed PTSD, or performance on the virtual Morris water task.

CONCLUSION

While performing the virtual Morris water task, we note that whereas people with PTSD and age-matched controls do not differ in performing the

TABLE 1. TALAIRACH TABLE AT $P = 0.01$, UNCORRECTED, FOR BOTH PATIENT AND CONTROL BRAIN ACTIVATIONS

Controls > patients Brain region	*Brodmann areas*	*Volume (cc)*		*Max T (x,y,z)*	
		L	*R*	*L*	*R*
Superior Temporal Gyrus	38	0.1	0.4	2.6(-62,-11,6)	3.9(30,13,-31)
Uncus	36,28	0	0.9	N.S.	3.4(27,4,-30)
ParaHPC Gyrus, HPC	35	0	0.4	N.S.	3.3(24,-10,-22)
Middle Temporal Gyrus	38,20,21	0.1	0.3	2.6(-62,-15,-12)	3.0(33,1,-38)
Middle Frontal Gyrus		0.1	0	2.7(-27,20,40)	N.S.
Inferior Frontal Gyrus		0.1	0	2.7(-53,32,-4)	N.S.
Superior Frontal Gyrus	8	0.2	0	2.7(-15,46,42)	N.S.

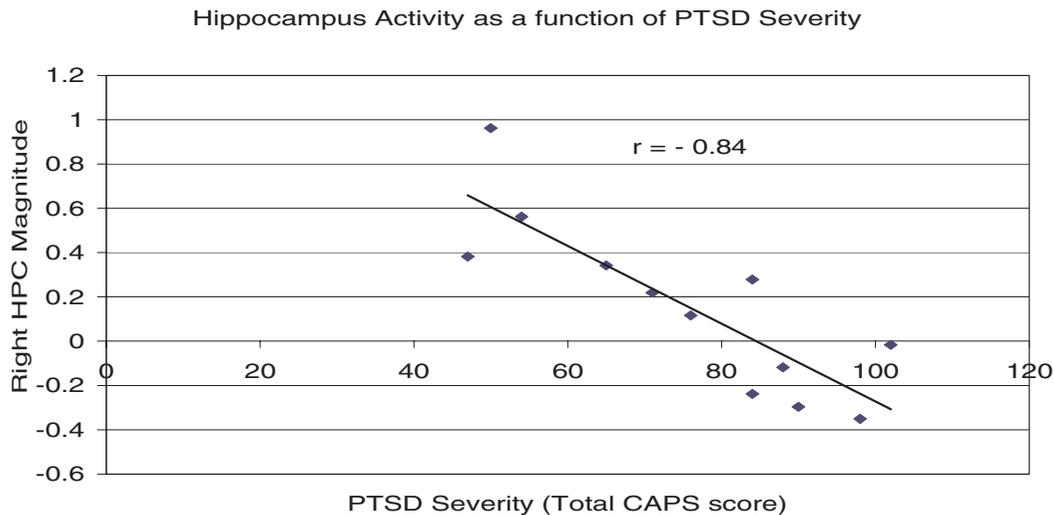Hippocampus Activity as a function of PTSD Severity

FIG. 3. Correlation between fMRI-derived HPC magnitude and CAPS symptom severity index.

task, there are significant differences in HPC involvement. Specifically, we note right HPC activity in the control group, but no HPC activity for the people with PTSD. This HPC involvement is consistent with our previous studies reporting that the virtual Morris water task can reliably activate the HPC, which is predicted from the nonhuman literature.[24,25,28,29]

It is interesting that the PTSD group did not show significant HPC activations during this task, and yet could perform the task. It may be that the chronic stress of PTSD has damaged their HPC, and hence, the neurons are not involved in this task as much as would be normal. However, it is unlikely that there exists massive HPC damage, because not only can the PTSD participants perform the task, but they do not display global memory dysfunction, which would be predicted following bilateral HPC damage. An alternative explanation is that the HPC is involved for this group, but that more subjects are needed for this activation to become significant. We currently are enrolling more subjects into the study as they become available to address this possibility.

Another possible explanation for this HPC dysfunction is offered by examining the strong correlations with the CAPS sub-score, the hyper-arousal score. Specifically, those who had higher levels of hyper-arousal had weaker HPC activations. It has been reported that people with PTSD have elevated amygdala responses,[30–34] and this may contribute to the hyper-arousal behaviors. Interestingly, it has

been reported that the amygdala has a direct competitive interaction with the HPC, so that when the amygdala activates, the HPC is inhibited.[35] Hence, in effect, those with strong hyper-arousal activity may have inhibited HPC activity. Future experiments are underway in our laboratory to assess HPC and amygdala interactions during fMRI.

Within the field of PTSD research, it is not clear whether HPC abnormalities are a consequence of the chronic stress of PTSD or are a preexisting risk factor for developing PTSD.[17] If indeed a dysfunctional HPC is a risk factor for developing PTSD, assessing HPC function after a trauma may indicate who is at risk for PTSD, and more aggressive therapies might be initiated to prevent its development. Moreover, assessment of HPC function could be used to predict which people are more resilient to developing PTSD if their jobs necessitate being exposed to traumas, such as the case with firefighters, police officers, and Special Forces military personnel. Utilizing a virtual Morris water task during fMRI can be a valuable tool in achieving these goals.

REFERENCES

1. Breslau, N., Kessler, R.C., et al. (1998). Trauma and posttraumatic stress disorder in the community: the 1996 Detroit Area Survey of Trauma. *Archives of General Psychiatry* 55:626–632.

2. Yehuda, R. (2004). Risk and resilience in posttraumatic stress disorder. *Journal of Clinical Psychiatry* 1:29–36.

3. Hedges, D.W., Allen, S., et al. (2003). Reduced hippocampal volume in alcohol and substance naive Vietnam combat veterans with posttraumatic stress disorder. *Cognitive & Behavioral Neurology* 16:219–224.

4. Schuff, N., Neylan, T.C., et al. (2001). Decreased hippocampal N-acetylaspartate in the absence of atrophy in posttraumatic stress disorder. *Biological Psychiatry* 50:952–959.

5. Gurvits, T.V., Shenton, M.E., et al. (1996). Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. *Biological Psychiatry* 40:1091–1099.

6. Squire, L.R., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science* 253:1380–1386.

7. O'Keefe, J., & Nadel, L. (1978). *The Hippocampus as a cognitive map*. Oxford, Clarendon Press.

8. Eichenbaum, H., & Cohen, N.J. (2003). From conditioning to conscious recollection: Memory systems of the brain. *London: Oxford University Press (2001) x, 583 pp*.

9. Cohen, N.J., & Eichenbaum, H. (1993). Memory, amnesia, and the hippocampal system. *Cambridge, MA, US: The MIT Press (1993) xii, 330 pp*.

10. Sapolsky, R.M., Uno, H., et al. (1990). Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *Journal of Neuroscience* 10:2897–2902.

11. Bremner, J.D., Randall, P., et al. (1997). Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse—a preliminary report. *Biological Psychiatry* 41:23–32.

12. Bremner, J.D. (2001). Hypotheses and controversies related to effects of stress on the hippocampus: an argument for stress-induced damage to the hippocampus in patients with posttraumatic stress disorder. *Hippocampus* 11:75–81.

13. Bremner, J.D. (2002). Neuroimaging studies in posttraumatic stress disorder. *Current Psychiatry Reports* 4:254–263.

14. Bremner, J.D. (2003). Long-term effects of childhood abuse on brain and neurobiology. *Child & Adolescent Psychiatric Clinics of North America* 12:271–292.

15. Schuff, N., Marmar, C.R., et al. (1997). Reduced hippocampal volume and n-acetyl aspartate in posttraumatic stress disorder. *Annals of the New York Academy of Sciences* 821:516–520.

16. Stein, M.B., Koverola, C., et al. (1997). Hippocampal volume in women victimized by childhood sexual abuse. *Psychological Medicine* 27:951–959.

17. Gilbertson, M.W., Shenton, M.E., et al. (2002). Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nature Neuroscience* 5:1242–1247.

18. Villarreal, G., & King, C.Y. (2004). Neuroimaging Studies Reveal Brain Changes in Posttraumatic Stress Disorder. *Psychiatric Annals* 34:845–856.

19. Pitman, R.K., Shin, L.M., et al. (2001). Investigating the pathogenesis of posttraumatic stress disorder with neuroimaging. *Journal of Clinical Psychiatry* 17:47–54.

20. Sutherland, R.J., Kolb, B., et al. (1982). Cortical noradrenaline depletion eliminates sparing of spatial learning after neonatal frontal cortex damage in the rat. *Neuroscience Letters* 32:125–130.

21. Bingman, V. (1988). Unimpaired acquisition of spatial reference memory, but impaired homing performance in hippocampal ablated pigeons. *Behavioral Brain Research* 27:179–188.

22. McNaughton, B.L., Barnes, C.A., et al. (1989). Hippocampal granule cells are necessary for normal spatial learning but not for spatially-selective pyramidal cell discharge. *Experimental Brain Research* 76:485–496.

23. Eichenbaum, H. (1994). The hippocampal system and declarative memory in humans and animals: Experimental analysis and historical origins. *Schacter, Daniel L (Ed); Tulving, Endel (Ed)* (1994). Memory systems 1994. (pp. 147–201). Cambridge: US: The MIT Press.

24. Astur, R.S., Taylor, L.B., et al. (2002). Humans with hippocampus damage display severe spatial memory impairments in a virtual Morris water task. *Behavioural Brain Research* 132:77–84.

25. Astur, R.S., St. Germain, S., Mathalon, D.H., et al. (2004). Using virtual reality to investigate the functioning of the hippocampus in schizophrenia. (*Cybertherapy Abstracts*).

26. Astur, R.S., St. Germain, S.A., et al. (2005). Hippocampal BOLD Responses during a Virtual Morris Water Task. Cognitive Neuroscience Abstracts.

27. Blake, D.D., Weathers, F.W., et al. (1995). The development of a Clinician-Administered PTSD Scale. *Journal of Traumatic Stress* 8:75–90.

28. Astur, R.S., Ortiz, M.L., et al. (1998). A characterization of performance by men and women in a virtual Morris water task: a large and reliable sex difference. *Behavioural Brain Research* 93:185–190.

29. Astur, R.S., Tropp, J., et al. (2004). Sex differences and correlations in a virtual Morris water task, a virtual radial arm maze, and mental rotation. *Behavioural Brain Research* 151:103–15.

30. Liberzon, I., Taylor, S.F., et al. (1999). Brain activation in PTSD in response to trauma-related stimuli. *Biological Psychiatry* 45:817–826.

31. Pissiota, A., Frans, O., et al. (2002). Neurofunctional correlates of posttraumatic stress disorder: a PET symptom provocation study. *European Archives of Psychiatry & Clinical Neuroscience* 252:68–75.

32. Rauch, S.L., van der Kolk, B.A., et al. (1996). A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. *Archives of General Psychiatry* 53:380–387.

33. Rauch, S.L., Whalen, P.J., et al. (2000). Exaggerated amygdala response to masked facial stimuli in post-

traumatic stress disorder: a functional MRI study. *Biological Psychiatry* 47:769–776.

34. Shin, L.M., McNally, R.J., et al. (1997). A positron emission tomographic study of symptom provocation in PTSD. *Annals of the New York Academy of Sciences* 821:521–523.

35. White, N.M., & McDonald, R.J. (2002). Multiple parallel memory systems in the brain of the rat. Neurobiology of Learning & Memory 77:125–184.

Address reprint requests to:
Dr. Robert S. Astur
Olin Neuropsychiatry Research Center
Institute of Living
200 Retreat Ave.
Hartford, CT 06106

E-mail: rastur@harthosp.org