npg

Left Orbital Frontal Cortex Volume and Performance on the Benton Visual Retention Test in Older Depressives and Controls

David C Steffens*,[1], Douglas R McQuoid[1], Kathleen A Welsh-Bohmer[1,2] and K Ranga Rama Krishnan[1]

[1]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA; [2]Joseph and Kathleen Bryan Alzheimer's Disease Research Center, Duke University Medical Center, Durham, NC, USA

Changes within the prefrontal cortex (PFC) have been associated with both mood disorders and with specific impairments in cognitive testing. The left PFC has been implicated in relational processing, that is, binding different pieces of information. We hypothesized that among older depressives and elderly controls, lower performance on one test of relational processing would be associated with smaller volume of the orbital frontal cortex (OFC). A total of 30 depressed and 40 control subjects were included in the study. All subjects were administered the Benton Visual Retention Test (BVRT). Subjects received a standardized magnetic resonance imaging, for which volumes of the OFC and total brain were calculated. We found that, controlling for age and education, total correct on BVRT was associated with left OFC volume normalized for total brain volume among the entire sample. For the depressed sample only, the number of perseverative errors was negatively associated with left OFC volume normalized for total brain volume after controlling for age and education. These results add to the literature linking mood and cognitive disturbances to the PFC. Future studies with a larger sample employing functional measures are warranted.
Neuropsychopharmacology (2003) 28, 2179–2183, advance online publication, 8 October 2003; doi:10.1038/sj.npp.1300285

INTRODUCTION

The prefrontal cortex (PFC) is one of several brain regions reported to be associated with mood disorders. The PFC plays an important role in information processing and integration. As a function of this region, both cognitive and emotional stimuli are evaluated, facilitating flexibility in decision-making and allowing the individual to respond adaptively to environmental cues and changes. Neuroimaging studies have linked the development of mood disorders with specific structures within the PFC, including the dorsolateral PFC, the anterior cingulate cortex, and the orbital frontal cortex (OFC). The volume of the OFC has been shown to be smaller in geriatric depression (Lai *et al*, 2000), and a smaller OFC volume was associated with functional impairment in depressives and controls (Taylor *et al*, 2003).

*Correspondence: Dr DC Steffens, Division of Geriatric Psychiatry, Duke University Medical Center, Box 3903, Durham, NC 27710, USA, Tel: +1 919 684 3746, Fax: +1 919 681 7668,
E-mail: steff001@mc.duke.edu

Better understanding of OFC function is thus likely to inform us about depression, particularly in the area of late-life depression. Previous studies in the neuroscience literature have implicated the left PFC in relational processing, which can be thought of as the binding of different pieces of information (Badgaiyan *et al*, 2002). Several experiments found increased activation in the left PFC during relational retrieval tasks (Mottaghy *et al*, 1999; Rugg *et al*, 1999; Simons *et al*, 2001). A recent study reported that the left inferior PFC was associated with retrieval on both the individual items that are necessary for relational retrieval and the link between these items (Badgaiyan *et al*, 2002). Ventromedial frontal lobe damage has been shown to increase false recognition and intrusion errors (Parkin *et al*, 1996). Damage to the dorsolateral PFC does not produce these errors (Schacter *et al*, 1998).

Based on these studies, we sought to characterize the relationship between OFC volume and cognitive function in depressed and nondepressed elders. We specifically examined performance on the Benton Visual Retention Test (BVRT) (Benton, 1974), a widely used instrument that assesses visual perception, visual memory, and visuoconstructive abilities. As it measures perception of spatial relations and memory for newly learned material, the BVRT

requires intact memory and relational processing. Subjects with impairment in these areas tend to make perseverative errors on the BVRT. We hypothesized that, among depressives, smaller left OFC volumes would be associated with greater numbers of perseverative errors on the BVRT and negatively associated with the BVRT total correct score.

MATERIALS AND METHODS

Sample

All subjects were participants in the National Institute of Mental Health—sponsored Duke University Mental Health Clinical Research Center (MHCRC) for the Study of Depression in Later Life. The patient group was restricted to subjects 60 years or older with a diagnosis of major depressive disorder. Exclusion criteria included (1) another major psychiatric illness; (2) current or past alcohol or drug dependence; (3) primary neurologic illness, including dementia; (4) medications or medical illness that would prevent the participants from completing neuropsychological testing (eg sedation from narcotic medications, severe visual impairment); (5) physical disability that precluded cognitive testing; and (6) metal in the body that precluded magnetic resonance imaging (MRI).

Control subjects were recruited from a listing of over 1900 community dwelling elders from the Aging Center Subject Registry at Duke University; these individuals have expressed a willingness to participate in the Duke Aging Center Research. Eligible control subjects had a nonfocal neurological examination, no self-report of neurological or depressive illness, and no evidence of a depression diagnosis based on the Diagnostic Interview Schedule (DIS; Robins *et al*, 1981) portion of the Duke Depression Evaluation Schedule (Landerman *et al*, 1989).

The Duke University Institutional Review Board (IRB) approved this study. The study's purpose and procedures were explained to all subjects; those providing written informed consent were enrolled.

Assessment Procedures

At baseline, a study geriatric psychiatrist administered a standardized clinical assessment to each subject. The assessment included the Montgomery–Asberg Depression Rating Scale (Montgomery and Asberg, 1979) and the Mini-Mental State Examination (Folstein *et al*, 1975). A trained interviewer administered the DIS to all subjects to assess symptoms of major depression.

Cognitive Assessment

Subjects were administered the BVRT (Benton, 1974) as part of a larger assessment battery that included the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery (Morris *et al*, 1989) and digit span forward and backward. The BVRT consists of 10 cards, each consisting of one or more simple geometric designs. The card is exposed for 10 s, and the subject must draw what he saw immediately after its removal. The test requires spatial conceptualization, immediate recall, and visuomotor reproduction. We chose to examine the BVRT

because it was one test in our battery in which we identified and counted perseverative errors.

MRI Variables

MRI acquisition. All subjects were screened for the presence of cardiac pacemakers, neurostimulators, metallic implants, metal in the orbit, aneurysm clips, or any other condition for which MRI was contraindicated. Subjects were imaged with a 1.5-T whole-body Signa MRI system (GE Medical Systems, Milwaukee, WI) using the standard head (volumetric) radiofrequency coil. Padding was used to immobilize the head without causing discomfort. The scanner alignment light was used to adjust the head tilt and rotation so that the axial plane lights passed across the cantho-meatal line, and the sagittal lights were aligned with the center of the nose. A rapid sagittal localizer scan was acquired to confirm the alignment. A dual-echo, fast spin-echo acquisition was obtained in the axial plane for morphometry of cerebral structures. The pulse sequence parameters were repetition time = 4000 ms, echo time = 30, 135 ms, 32 kHz ($\pm$ 16 kHz) full imaging bandwidth, echo train length = 16, a 256 × 256 matrix, 3-mm section thickness, one excitation and a 20-cm field of view. The images were acquired in two separate acquisitions, with a 3-mm gap between sections for each acquisition. The second acquisition was offset by 3 mm from the first so that the resulting data set consisted of contiguous sections.

MRI processing. Images were archived as a normal procedure on magneto-optical disks in the MRI center and transferred to the Duke Neuropsychiatric Imaging Research Laboratory (NIRL) for processing on SUN workstations. Volume measurements used an NIRL-modified version of MrX Software, which was created by GE Corporate Research and Development (Schnectady, NY) and originally modified by Brigham and Women's Hospital (Boston, MA) for image segmentation.

The basic segmentation protocol is a supervised, semi-automated method that has been described previously (Byrum *et al*, 1996; Kikinis *et al*, 1992). Once the brain was segmented into tissue types and the nonbrain tissue stripped away through a masking procedure, the total hemispheric gray and white matter volumes were calculated. The total left and right gray and white matter volume was defined as the total brain volume.

Next, specific regions of interest (ROIs) were assessed using tracing and connectivity functions. The medial OFC was traced bilaterally, and a mask was created and applied to the segmented brain. The neuroanatomic borders of the OFC used for this study have been previously described (Lai *et al*, 2000). To summarize the method briefly, the *inferior* border begins with the first appearance of the frontal lobe tissue as one moves superiorly from the base of the brain on consecutive axial slices. As one moves superiorly, the limen insula (temporal stem) appears connecting the orbital frontal gyrus (OFG) and temporal lobes. The *posterior* boundary of OFG was determined by the anterior appearance of the circular insular sulcus. If the cistern of the cerebral vallecula was greater than or equal to 20 pixels across, then lines were drawn from the circular insular sulcus to the lateral end of the cistern of the cerebral

vallecula on each hemisphere. If the cistern was less than 20 pixels across, then a line was drawn joining the circular insular sulci of each hemisphere. The entire *lateral* extent of the frontal lobe was included until the superior border was reached. To determine the most *superior* slice to include in the OFG, each hemisphere was assessed separately. If the cerebrospinal fluid of the olfactory sulcus plus the gray matter extending posteriorly from the sulcus was at least 3/4 of the OFG length (anterior to posterior), the OFG was included in that hemisphere.

The final step was to run a summarizing program that calculated the volume within the specific OFC ROI defined by the analyst.

All technicians received extensive training by experienced volumetric analysts. Reliability was established by repeated measurements on multiple MRI scans before raters were approved to process the study data. Intraclass correlation coefficients were as follows: total brain = 0.998, left medial OFC = 0.9, and right medial OFC = 0.9.

Analytic Strategy

Bivariate analyses were performed on variables comparing means and proportions of patients to those of controls from the study. Group differences for categorical variables were analyzed using the χ^2 test for sex and Fisher's exact test for race. For all continuous variables a *t*-test was used to compare means between groups.

A series of linear regression models were constructed to test the relationship between BVRT perseverative errors and the proportion of OFC (left, right, and total) volume to the total brain volume (ie normalized OFC volumes). We decided *a priori* to control for the effects of age and years of education in all regression models because these factors are known to independently affect performance on the BVRT. While sex differences have also been shown for some neuropsychological tests, sex may not affect BVRT performance in the elderly (Coman *et al*, 1999), so we decided not to automatically include it *a priori* in our models.

Similar models were constructed with number correct on BVRT as the independent variable.

RESULTS

The sample consisted of 30 depressed and 40 nondepressed control subjects. As shown in Table 1, the mean age for both groups was about 70 years. The control group had significantly more female subjects than the depressed group. The two groups did not differ significantly by race, education, or MMSE score. The mean MADRS score for the depressed group was 26.67 (± 5.66).

Table 1 also shows performance on BVRT and MRI brain volumes. The control group had a higher total correct score on the BVRT than the depressed group, a statistically significant difference. There was no difference in the number of perseverative errors between groups. The control group had larger volumes of left, right, and total OFC, although the difference for right OFC was not statistically significant. There was no difference in the total brain volume between the two groups.

We performed a series of regression models to examine the associations between BVRT performance and left, right, and total OFC volume normalized for (divided by) the total brain volume. Included in the models were total correct on BVRT, with age and education also included as covariates. We examined depressives, controls as well as both groups combined ($N = 70$). We then did the same for BVRT perseverative errors, also controlling for age and education.

In none of the models was BVRT performance (correct or perseverations) significantly associated with either total or right normalized OFC volume. We present the results examining the relationship between BVRT performance and left normalized OFC volume.

In a regression model (see Table 2) controlling for the effects of age and education, left OFC volume (normalized for total brain volume) was associated with total correct on BVRT for the entire sample. In separate models of normalized left OFC volume (not shown), when we

Table 1 Sample Characteristics and Between-Group Comparisons

	Total sample (*N* = 70)	Depressed (*N* = 30)	Controls (*N* = 40)	Test statistic, df, *p*-value
Age, mean (SD)	70.34 (6.57)	69.60 (7.15)	70.90 (6.13)	$t = 0.82$, df = 68, $p = 0.42$
Sex, *N* (%) female	49 (70.00)	16 (53.33)	33 (82.50)	$\chi^2 = 6.944$, df = 1, $p = 0.008$
Race				Fisher's exact test, $p = 0.087$
% Caucasian	59 (84.29)	23 (76.67)	36 (90.00)	
% African American	10 (14.29)	7 (23.33)	3 (7.50)	
% Other race	1 (1.43)	0 (0.00)	1 (2.50)	
Education (years), mean (SD)	15.01 (3.11)	14.30 (3.58)	15.55 (2.62)	$t = 1.69$, df = 68, $p = 0.096$
Mini–Mental State Examination, mean (SD)	28.80 (1.28)	28.47 (1.48)	29.05 (1.05)	$t = -1.84$, df = 50.1 (unequal variances) $p = 0.0712$
BVRT, total correct, mean (SD)	5.96 (2.18)	4.97 (2.48)	6.7 (1.59)	$t = 3.34$, df = 46.3, $p = 0.002$
BVRT, perseverative errors, mean (SD)	0.73 (0.95)	0.67 (0.96)	0.78 (0.95)	$t = 0.47$, df = 68, $p = 0.639$
Left OFC volume (ml), mean (SD)	6.29 (1.48)	5.85 (1.57)	6.62 (1.32)	$t = 2.23$, df = 68, $p = 0.029$
Right OFC volume (ml), mean (SD)	6.79 (1.58)	6.41 (1.82)	7.05 (1.33)	$t = 1.71$, df = 68, $p = 0.093$
Total OFC volume (ml), mean (SD)	13.07 (2.84)	12.26 (3.21)	13.68 (2.39)	$t = 2.12$, df = 68, $p = 0.038$
Total brain volume (ml), mean (SD)	1007.23 (122.46)	1031.5 (144.03)	989.07 (101.57)	$t = 1.38$, df = 49.5, $p = 0.175$

Table 2 Linear Regression Models of the Left Orbital Frontal Cortex Volume, Normalized for Total Brain Volume for the Entire Sample

	Estimate (SE) ($\times 10^4$)	t-Value	p-Value
Age	0.2888 (0.2557)	1.13	0.2628
Education	−0.4843 (0.7148)	−0.68	0.5004
BVRT—total correct	1.9012 (0.9677)	2.21	0.0309

Table 3 Linear Regression Models of the Left Orbital Frontal Cortex Volume, Normalized for Total Brain Volume for Depressed Patients Only

	Estimate (SE) ($\times 10^4$)	t-Value	p-Value
Age	−0.0605 (0.2757)	−0.22	0.8281
Education	−0.7958 (0.6421)	−1.24	0.2262
BVRT—perseverative errors	−4.6544 (2.0262)	−2.30	0.0299

examined the groups separately, BVRT total correct was not significant ($p < 0.172$ for depressed and $p < 0.556$ for controls).

In another regression model (see Table 3) involving the depressed patients only, when we controlled for the effects of age and education, left OFC volume (normalized for total brain volume) was associated with total perseverative errors on BVRT. In a separate model (not shown), when the depressed and control groups were combined, perseverative errors were not significant ($p < 0.564$).

As our regression models were significant only for left normalized hippocampal volume, we present a summary of *post hoc* bivariate analyses examining MMSE, MADRS, and sex effects on left normalized hippocampal volume. For the entire group, the total MMSE score was associated with total BVRT correct ($p < 0.0001$), but not with the number of perseverative errors ($p < 0.2400$) or left normalized OFC volume ($p < 0.6380$). Sex was not associated with BVRT total correct ($p < 0.8040$), perseverative errors ($p < 0.9816$), or with left normalized OFC volume ($p < 0.8101$). For the depressed group, the total MADRS score was not associated with total correct on BVRT ($p < 0.1598$), BVRT perseverative errors ($p < 0.4476$), or with left normalized OFC volume ($p < 0.7689$). Among depressives, the MMSE score was associated with BVRT total correct ($p < 0.001$), but it was not associated with perseverative errors ($p < 0.6704$) or with left normalized OFC volume ($p < 0.2860$). Sex was associated with left normalized OFC volume ($p < 0.0083$), but it was not associated with BVRT total correct ($p < 0.1250$) or perseverative errors ($p < 0.0988$).

We then constructed subsequent models controlling for sex effects. For the entire sample, the BVRT number correct remained significantly associated with left normalized OFC volume after controlling for age, sex, and education ($p < 0.0376$). Among patients, when sex was added as a covariate along with age and education, the association between number of perseverative errors on BVRT and normalized left OFC volume fell short of significance ($p < 0.0746$).

Discussion

The major finding of this study was that the left OFC volume was associated with performance on the BVRT, both total score and number of perseverative errors. The results remained statistically significant after controlling for the effects of age and education. Total correct on BVRT was significant for the entire sample, and, although it did not reach statistical significance ($p < 0.172$), the trend was similar for the 30 depressed patients. Conversely, among the depressed patients, perseverative errors were significantly associated with left OFC volumes controlling for age and education.

These results are consistent with findings in the neuroscience literature linking the left PFC with relational processing, in particular with retrieval of relevant information during episodic memory tasks (Badgaiyan *et al*, 2002). Activation of the left inferior PFC has been reported during retrieval experiments (Mottaghy *et al*, 1999; Rugg *et al*, 1999; Simons *et al*, 2001) and during encoding tasks (Dolan and Fletcher, 1997; Mottaghy *et al*, 1999). A recent functional MRI study found activity in the left PFC when participants thought about a just-seen item and in the right PFC when participants noted whether an item had been presented previously (Johnson *et al*, 2003).

Several neuroscience studies have focused specifically on the OFC. One study reported that the processing of stimuli that deviate from expectations involves the OFC selectively (Petrides *et al*, 2002). In contrast, they found that when subjects make explicit decisions on the contents of memory (eg judgments of relative stimulus familiarity), the mid-ventrolateral PFC is involved, and that the mid-dorsolateral PFC is engaged in tasks requiring monitoring of information within working memory. Another functional study using positron emission tomography showed that the left OFC was activated during recall of both novel and practiced unrelated words, while the right OFC was relatively more active during recall of the practiced but not the novel word list (Paradiso *et al*, 1997). These authors suggested that the left OFC might have a specific role in the retrieval of unstructured verbal information.

The present study also adds to the literature linking geriatric depression with the OFC. As neuroscience studies improve understanding of this brain structure, new findings will better inform research in late-life depression and its cognitive consequences. Clinical correlation of relational processing associated with OFC dysfunction may include many of the previously reported problems associated with executive dysfunction in geriatric depression such as loss of interest in activities and naming difficulties (Alexopoulos *et al*, 2002). These cognitive changes may be associated with functional impairment seen in late-life depression (Kiosses *et al*, 2001; Steffens *et al*, 1999).

Other studies have examined type of error on neuropsychological testing in depression and dementia. Demented patients, compared with controls, have been reported to have greater perseverations and omissions (Eslinger *et al*, 1988). Omissions are reported as most discriminating of depression when compared to dementia (La Rue *et al*, 1986). Our findings indicate that, in addition to dementia, perseverative errors are important in late-life depression as well. Future studies would need to determine if the left

orbital frontal volume is reduced in both demented and depressed elderly subjects who commit perseverative and other types of errors.

Future research should also include larger samples of depressed patients. It is likely that our sample of 30 depressed patients was not large enough to detect a significant association between total correct on the BVRT and normalized left OFC volume among the depressed group only. Our study focuses on one test in a relatively small sample, so our results should be viewed with a cautious eye. Future research will need to include other clinical neuropsychological measures that assess memory and relational processing. Our study focused on structural imaging; future studies on late-life depression should also include a functional imaging component.

ACKNOWLEDGEMENTS

REFERENCES

Alexopoulos GS, Kiosses DN, Klimstra S, Kalayam B, Bruce ML (2002). Clinical presentation of the 'depression-executive dysfunction syndrome' of late life. *Am J Geriatr Psychiatry* **10**: 98–106.

Badgaiyan RD, Schacter DL, Alpert NM (2002). Retrieval of relational information: a role for the left inferior prefrontal cortex. *Neuroimage* **17**: 393–400.

Benton A (1974). *Revised Visual Retention Test: Clinical and Experimental Applications* 4th edn Psychological Corporation: New York, NY.

Byrum CE, MacFall JR, Charles HC, Chitilla VR, Boyko OB, Upchurch L et al (1996). Accuracy and reproducibility of brain and tissue volumes using a magnetic resonance imaging segmentation method. *Psychiatry Res* **67**: 215–234.

Coman E, Moses JA, Kraemer HC, Friedman L, Benton AL, Yesavage J (1999). Geriatric performance on the Benton Visual Retention Test: demographic and diagnostic considerations. *Clin Neuropsychol* **13**: 66–77.

Dolan RJ, Fletcher PC (1997). Dissociating prefrontal and hippocampal function in episodic memory coding. *Nature* **388**: 582–585.

Eslinger PE, Pepin P, Benton AL (1988). Different patterns of visual memory errors occur with aging and dementia. *J Clin Exp Neuropsychol* **10**: 60–61 (abstract).

Folstein MF, Folstein SE, McHugh PR (1975). Mini-Mental state. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**: 189–198.

Johnson MK, Raye CL, Mitchell KJ, Greene EJ, Anderson AW (2003). FMRI evidence for an organization of prefrontal cortex by both type of process and type of information. *Cereb Cortex* **13**: 265–273.

Kikinis R, Shenton ME, Gerig G, Martin J, Anderson M, Metcalf D et al (1992). Routine quantitative analysis of brain and cerebrospinal fluid spaces with MR imaging. *J Magn Reson Imaging* **2**: 619–629.

Kiosses DN, Klimstra S, Murphy C, Alexopoulos GS (2001). Executive dysfunction and disability in elderly patients with major depression. *Am J Geriatr Psychiatry* **9**: 269–274.

Lai T-J, Payne M, Byrum CE, Steffens DC, Krishnan KRR (2000). Reduction of orbital frontal cortex volume in geriatric depression. *Biol Psychiatry* **48**: 971–975.

La Rue A, D'Elia LF, Clarke EO, Spar JE, Jarvik LF (1986). Clinical tests of memory in dementia, depression, and healthy aging. *J Psychol Aging* **1**: 69–77.

Landerman R, George LK, Campbell RT, Blazer DG (1989). Alternative models of the stress buffering hypothesis. *Am J Commun Psychol* **17**: 626–642.

Montgomery SA, Asberg M (1979). A new depression scale designed to be sensitive to change. *Br J Psychiatry* **134**: 382–389.

Morris JC, Heyman A, Mohs RC, Hughes JP, Van Belle G, Fillenbaum G et al (1989). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD), I: clinical and neuropsychological assessment of Alzheimer disease. *Neurology* **39**: 1159–1165.

Mottaghy FM, Shah NJ, Krause BJ, Schmidt D, Halsband U, Jancke L et al (1999). Neuronal correlates of encoding and retrieval in episodic memory during a paired-word association learning task: a functional magnetic resonance imaging study. *Exp Brain Res* **128**: 332–342.

Paradiso S, Crespo Facorro B, Andreasen NC, O'Leary DS, Watkins LG, Boles Ponto L et al (1997). Brain activity assessed with PET during recall of word lists and narratives. *Neuroreport* **8**: 3091–3096.

Parkin AJ, Bindschaedler C, Harsent L, Metzler C (1996). Pathological false alarm rates following damage to the left frontal cortex. *Brain Cogn* **32**: 14–27.

Petrides M, Alivisatos B, Frey S (2002). Differential activation of the human orbital, mid-ventrolateral, and mid-dorsolateral prefrontal cortex during the processing of visual stimuli. *Proc Natl Acad Sci USA* **99**: 5649–5654.

Robins N, Helzer JE, Croughan J, Ratcliff KS (1981). National Institute of Mental Health diagnostic interview schedule. *Arch Gen Psychiatry* **38**: 381–389.

Rugg MD, Fletcher PC, Chua PM, Dolan RJ (1999). The role of the prefrontal cortex in recognition memory and memory for source: an fMRI study. *Neuroimage* **10**: 520–529.

Schacter DL, Norman KA, Koutstaal W (1998). The cognitive neuroscience of constructive memory. *Annu Rev Psychol* **49**: 289–318.

Simons JS, Graham KS, Owen AM, Patterson K, Hodges JR (2001). Perceptual and semantic components of memory for objects and faces: a pet study. *J Cogn Neurosci* **13**: 430–443.

Steffens DC, Hays JC, Krishnan KR (1999). Disability in geriatric depression. *Am J Geriatr Psychiatry* **7**: 34–40.

Taylor WD, Steffens DC, McQuoid DR, Payne ME, Lee SH, Lai TJ et al (2003). Smaller orbital frontal cortex volumes associated with functional disability in depressed elders. *Biol Psychiatry* **53**: 144–149.