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A Tc-99m SPECT study of regional cerebral blood flow in patients with transient global amnesia

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ABSTRACT

Objectives: This study aimed to determine whether regional cerebral blood flow (rCBF) is abnormal in patients who have Transient Global Amnesia (TGA).
Methods: We obtained noninvasive rCBF measurements using Tc-99m-ethyl cysteinate diamer Single Photon Emission Computed Tomography (SPECT) in 7 patients diagnosed with TGA within 4 days of onset of the amnestic episode while the patients were still symptomatic and in 17 age-matched healthy control subjects. We assessed memory functioning using the Hopkins's Verbal Learning Test (HVLT) and Statistical Parametric Mapping to compare rCBF across diagnostic groups.
Results: The patients with TGA were significantly impaired in their performance on the 20-minute delayed recall of the HVLT. They also exhibited significantly decreased rCBF on their SPECT scans in the inferior and middle frontal gyrus bilaterally, with more prominent left-sided reductions in the superior temporal, precentral, and postcentral gyri, as well as increased rCBF primarily in the right hemisphere within the middle temporal, superior temporal, and inferior frontal gyri, cerebellum, and thalamus, compared with the normal control group.
Conclusion: These findings suggest that lateralized abnormalities in brain functioning are an important component of the pathophysiology of TGA. Lateralized abnormalities may disrupt functions that are relatively specific to the left hemisphere, including receptive language, symbolic representation, and the processing of local features in the environment, while preserving anterograde memory processes. Increased flow to the right hemisphere centered on regions that subserve the functions of expressive language and visuospatial processing, and may represent processes that compensate for flow reductions to the left hemisphere.
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Introduction

Transient Global Amnesia (TGA) is defined by a sudden onset of transient impairment of memory for recent events, a transient inability to retain new information, and retrograde amnesia in the absence of other neurological signs and symptoms. The annual incidence of TGA in the general population is approximately 3 per 100,000 people, with a peak incidence between the ages of 50 and 60 years (Schmidtke et al., 2002). Although its etiology is unknown, transient ischemic attacks, epilepsy, and migraines have been proposed as possible causes or precipitating events (Hodges and Oxbury, 1990a; Hodges and Ward, 1989).

Studies of cerebral perfusion during episodes of TGA may improve our understanding of the pathogenesis of TGA. Because TGA is both rare and short-lived, however, neuroimaging studies performed during or immediately following the attack of amnesia in close temporal proximity to the inciting cerebral event are also rare, the numbers of subjects in those studies have been small, and the findings thus far have been inconclusive (Asada et al., 2000; Evans et al., 1993; Jung et al., 1996; Schmidtke et al., 1998; Stillhard et al., 1990; Tanabe et al., 1991; Warren et al., 2000). Indeed, most studies have been performed remotely from the time of onset, long after the resolution of amnesia.

Previous imaging studies of cerebral perfusion in TGA have employed Region-of-Interest (ROI) analyses to detect abnormalities in cerebral blood flow (CBF). ROI analyses can suffer from inefficiency and inaccuracy in detecting abnormalities that are small relative to the size of the ROI or that extend across the boundaries of two or more ROIs. Voxel-based approaches largely avoid these difficulties when

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testing statistically for group differences, and they may in addition afford an advantage in diminishing operator bias (Furutani et al., 2005). Thus, voxel-based approaches such as Statistical Parametric Mapping (SPM) are now being applied increasingly in rCBF studies using Single Photon Emission Computed Tomography (SPECT) (Acton and Friston, 1998; Friston et al., 1991; Lingford-Hughes et al., 1998).

The aim of the present study was to identify disturbances of rCBF in TGA patients using SPM-based analyses. Seven patients who were recently diagnosed with TGA underwent Tc-99m-ethyl cysteinate diamer SPECT scanning 1–4 days from the onset of the acute amnestic episode and while they were still exhibiting memory disturbances. These rCBF maps were compared with those of 17 age-matched, healthy control subjects.

Methods

Subjects and characterization

Seven patients with TGA (M:F = 4:3, ages: 52–69 years, mean 63.4 ± 4.84 years, all right-handed) were recruited upon being diagnosed with TGA. The diagnosis was established using standard clinical diagnostic criteria[3] applied to a semi-structured interview and neurological exam developed in-house and administered by a senior neurologist. During the TGA episode, neurological examination disclosed no abnormalities or cognitive deficits other than amnesia. The Mini-Mental State Examination (MMSE) (Folstein et al., 1975) was performed after the initial diagnosis of TGA, and then the subtest assessing memory for three objects was repeated every 2 h during the patients' waking hours, using different objects upon each administration, to determine the time course of memory disturbance and recovery. Seventeen age-matched healthy controls (M:F = 7:10, ages: 56–69 years, mean 62.2 ± 6.84 years, all right-handed) were recruited through local advertisements They reported no psychiatric or neurological problems themselves or in their families, and no history of memory disturbance. The health of the normal control group was confirmed using a structured questionnaire for dementia (Christensen et al., 1991), the MMSE, and a clinical diagnostic interview. All participants denied any history of epilepsy, migraine, cerebral ischemic events, or drug use, and none were taking psychoactive medications.

The Hopkins's Verbal Learning Test (HVLT) (Brandt, 1991), shown previously to be of use in verifying the verbal memory impairment associated with TGA, was administered to the patient group immediately after the SPECT scan. The HVLT assesses verbal memory performance by measuring the recognition, immediate recall, and 20-minute delayed recall of 12 words read at random by the examiner from a larger list of 24 words belonging to 3 semantic categories, at a rate of 1 word every 2 s (Table 1).

All subjects gave informed written consent to participate, and the Institutional Review Board of the Catholic Medical Center in Seoul, South Korea, approved the study.

SPECT scanning

All subjects were scanned within 4 days from the onset of TGA (Table 1), as soon as serial examinations revealed resolution of their acute confusional state, at a time when they were capable of providing informed consent and cooperating with the scanning protocol. SPECT imaging was initiated 20 min after intravenous injection of approximately 740–925 MBq of Tc-99m-ECD (ethyl cysteinate diamer) using a multi-detector scanner (ECAM plus; Siemens, Erlangen, Germany) equipped with a low-energy, fan-beam collimator. The head unit consisted of two rotating rings of 59 probe-type detectors. Data were reconstructed in a 128 × 128 matrix with a pixel size of 3.9 × 3.9 × 3.9 mm (FOV = 240 mm, slices thickness = 7 mm) and a 20% symmetric window at 140 keV. Continuous transaxial tomograms of the brain were reconstructed after back-projection using a Butterworth filter (cutoff frequency 0.4 cycles/pixel, order 5) to reduce statistical noise. Tc-99 m ECD images were corrected for tissue attenuation using a standard commercial correction routine (Siemens Inc., Erlangen, Germany), assuming uniform attenuation and a circular head shape.

Image preprocessing

All subsequent image manipulation and data analyses were performed on an IBM personal computer running a Windows XP operating system. The software for image manipulation included Matlab version 5.3 (Mathworks, Inc., Natick, MA) and Statistical Parametric Mapping 99 (SPM99: Institute of Neurology, University College of London, UK) (Friston et al., 1995b). The SPECT data with attenuation and scatter correction were converted into ANALYZE format (Mayo Foundation, Baltimore, MD, USA) having voxel dimensions of 3.9 mm in each spatial dimension. The mean pixel intensity across all slices of the imaging volume was calculated. Each pixel was then thresholded at 80% of this value to eliminate background noise and partial volume effects at the edge of the brain. Each SPECT scan was then spatially normalized using a 12-parameter affine warp and sinc-linear interpolation to the SPECT template brain from the Montreal Neurological Institute (Friston et al., 1995a), reformatted to a 16-bit image having 79 × 95 × 68 voxels, each 2 × 2 × 2 mm in size. These images were spatially smoothed using a Gaussian filter of 16 mm Full-Width at Half Maximum. Normalized rCBF values were calculated by dividing CBF at each voxel by global CBF in each individual.

Table 1
Clinical and laboratory characteristics of TGA patients.

	TGA patient						
	1	2	3	4	5	6	7
Sex	M	F	M	M	M	F	F
Age	70	63	67	67	68	63	68
Time to recovery (hours)	7	17	14	12	10	12	16
Precipitating event	Physical abuse	Swimming	Emotional distress	Tennis playing	Emotional distress	Emotional distress	Cold stress
EEG	Normal	Normal	Normal	Normal	Normal	Normal	Normal
MRI	Normal	Normal	Normal	Normal	Normal	Normal	Normal
SPECT timing (days after TGA onset)	3	1	3	2	4	2	2
HVLT free recall	1 + 2 + 6 = 9 (15)	4 + 8 + 6 = 18(40)	NA	6 + 7 + 7 = 20 (40)	0 + 5 + 5 = 10 (25)	1 + 4 + 5 = 10 (30)	0 + 4 + 5 = 9 (35)
HVLT recognition index	9 − 4 = 5 (60)	7 − 2 = 5 (60)	NA	9 − 2 = 7 (70)	7 − 4 = 3 (30)	6 − 3 = 3 (30)	7 − 4 = 3 (30)

M = Male, F = Female.
HVLT, Hopkins Verbal Learning Test reported as percentile of clinical norms in parentheses; NA, not available.
HVLT Recognition (Discriminability) Index: true positive-false positive responses. Parentheses indicate percentile relative to clinical norms.
HVLT Free Recall: 1st + 2nd + 3rd recall = total.

Table 2
Anatomical sites of decreased rCBF in TGA patients compared with controls.

Regions	Abbreviation	Number of voxels in cluster	*t*-statistic (*z*-level)	Location (*x*, *y*, *z* mm)	Brodmann's area
Lt frontal lobe, Inferior frontal gyrus	IFG	5792	5.57 (4.04)	−52, 8, 30	9
Lt parietal lobe, Postcentral gyrus	PoCG	5792	5.30 (3.92)	−52, −20, 26	2
Lt frontal lobe, Middle frontal gyrus	MFG	5792	5.09 (3.82)	−34, 24, 40	8
Rt parietal lobe, Inferior parietal gyrus	IPG	202	4.71 (3.63)	40, −40, 42	40
Lt parietal lobe, Inferior parietal gyrus	IPG	398	4.22 (3.37)	−52, −42, 42	40
Lt frontal lobe, Precentral gyrus	PrCG	768	4.20 (3.36)	−24, −18, 60	6
Lt frontal lobe, Inferior frontal gyrus	IFG	248	3.94 (3.21)	−23, 31, −10	47
Rt frontal lobe, Inferior frontal gyrus	IFG	233	3.37 (2.86)	24, 31, −10	47
Lt cerebellum	Crb	234	3.32 (2.83)	−18, −50, −24	NA
Lt temporal lobe, Middle temporal gyrus	MTG	233	3.31 (2.83)	−58, −36, 6	37 (Wernicke's)

Lt = left; NA = not applicable.

Statistical analysis

Intensity-normalized SPECT data from the TGA group were compared with similarly normalized data from the 17 healthy subjects. Group contrasts in rCBF were estimated at each voxel using the General Linear Model of SPM99. A two-sample *t*-test model was fitted, and a *t*-statistic image was constructed and then thresholded at $t > 3.30$, corresponding to an uncorrected p-value < 0.01, in conjunction with a cluster filter of 200 voxels in the reformatted, template imaging space. This combined application of a statistical threshold and cluster filter has previously been shown to reduce substantially the false positive identification of activated pixels at any given threshold (Forman et al., 1995). For purposes of visualization and anatomic localization, the *t*-score clusters were projected onto the standard high-resolution T1-weighted MRI.

Results

The clinical characteristics of the participants and measures of their memory performance are summarized in Table 1. Diagnostic groups did not differ on age (Student's $t = 0.964$, $df = 6$, $p = 0.13$), gender ($t = 0.854$, $df = 6$, $p = 0.50$), or educational level ($t = 0.768$, $df = 6$, $p = 0.66$). Even after recovery from their acute confusional state, the TGA patients demonstrated grossly impaired 20-minute delayed recall relative to published norms, despite good preservation of verbal recognition memory, on the HVLT administered immediately after the SPECT scan. We therefore regard our SPECT findings as representing ongoing, intra-episode disturbances in neural functioning during the amnestic episode.

The mean global CBF for the TGA group (155.93 ± 10.81 counts/min) did not differ significantly from that of the controls (160.14 ± 15.87 counts/min) (Student's $t = -.475$, $df = 6$, $p = 0.65$). Voxel-wise comparisons of globally normalized rCBF across diagnostic groups revealed reduced flow in the TGA patients in the inferior and middle frontal gyrus bilaterally, with more prominent left-sided reductions in the superior temporal, precentral, and postcentral gyri (Table 2). Increases in rCBF were detected in the TGA patients primarily in the right hemisphere, within the right middle temporal, superior temporal, and inferior frontal gyri, and in the right cerebellum and right pulvinar nucleus of the thalamus (Table 3). These results therefore indicate in general that blood flow in the TGA patients was reduced in the left and increased in the right cerebral hemisphere relative to controls (Fig. 1). These lateralized findings were also evident in the individual rCBF maps of each of the 7 TGA patients compared with the controls (data not shown).

Discussion

This study demonstrated that within 4 days of the onset of amnesia—when serious impairment of delayed recall was still clearly present on detailed neuropsychological testing but after the resolution of the acute confusional state—rCBF in the patients with TGA was significantly increased in the broad expanses of the right hemisphere (in the right hemisphere homologue of Broca's region, in the temporal cortices, and thalamus), but significantly reduced in frontal cortices bilaterally and in the left hemisphere elsewhere (in pericentral, parietal, and temporal cortices, including Wernicke's region). To our knowledge, this is the first study to demonstrate prominent hemispheric specificity in abnormalities of cerebral blood flow during the period of continuing memory impairment within an amnestic episode of TGA.

Findings from previous functional imaging studies of TGA patients have been inconsistent and include abnormalities in perfusion of the temporal lobes (Asada et al., 2000; Evans et al., 1993; Jung et al., 1996; Matsuda et al., 1993; Schmidtke et al., 2002; Stillhard et al., 1990; Strupp et al., 1998; Tanabe et al., 1991; Warren et al., 2000), thalamus (Goldenberg et al., 1991; Sakashita et al., 1997; Schmidtke et al., 2002), and striatum (Baron et al., 1994; Schmidtke et al., 2002). Although most studies of TGA have reported decreased perfusion, hyperperfusion in persons with TGA has also been reported in a handful of studies, particularly in the hippocampus, amygdala, and thalamus of the left hemisphere (Asada et al., 2000; Jung et al., 1996; Matsuda et al., 1993). The inconsistency in findings across studies are probably attributable to differences in variability in patient characteristics, including the timing of scan acquisition relative to clinical recovery from the amnestic episode, the degree of ischemia present during the scan, and the presence of varying cognitive deficits during and after the episode (Baron et al., 1994; Eustache et al., 1997; Hodges and Oxbury, 1990a; Hodges and Warlow, 1990; Jung et al., 1996; Stillhard et al., 1990). Although the perfusion abnormalities detected after clinical

Table 3
Anatomical sites of increased rCBF in TGA patients compared with controls.

Regions	Abbreviation	Number of voxels in cluster	*t*-statistic (*z*-statistic)	Location (*x*, *y*, *z* mm)	Brodmann's area
Rt temporal lobe, Superior temporal gyrus	STG	1493	5.91 (4.18)	66, −42, 8	22
Brain stem, midbrain	MB	240	5.82 (4.15)	2, −30, −16	NA
Rt occipital lobe, Lingual gyrus	LG	1842	5.39 (3.96)	4, −90, −12	NA
Rt thalamus, pulvinar	Pulv	243	4.58 (3.57)	18, −24, 6	NA
Rt temporal lobe, Middle temporal gyrus	MTG	1493	4.36 (3.44)	66, −32, 0	21
Rt frontal lobe, Inferior frontal gyrus	IFG	1493	4.28 (3.41)	60, 26, 0	45 (Broca's)
Rt cerebellum	Crb	520	4.03 (3.25)	40, −84, −20	NA

Rt = right; NA = not applicable.

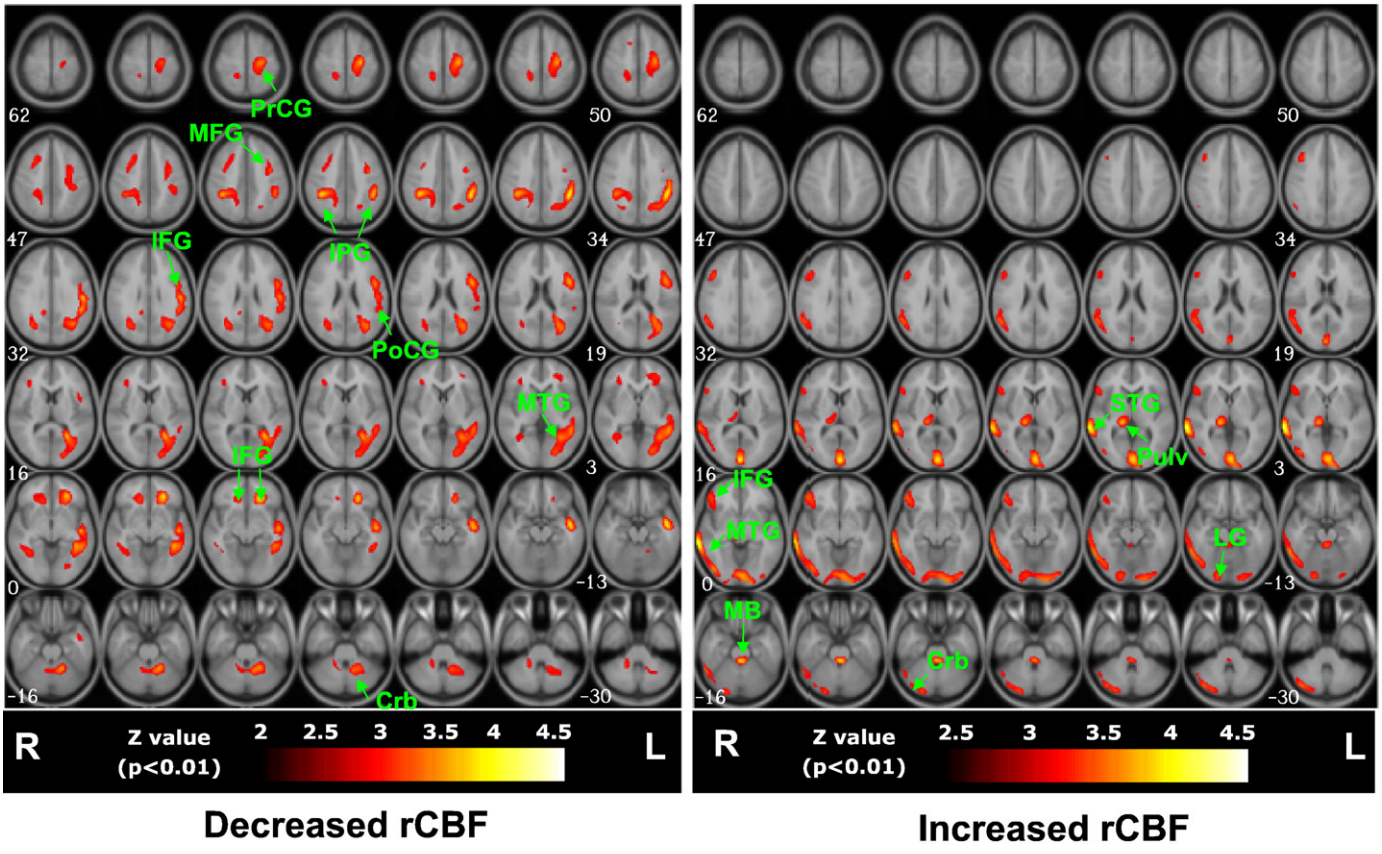

Fig. 1. Group comparisons of regional CBF significant differences in voxel-wise comparisons of rCBF across groups (thresholded at $p<0.01$) are superimposed on T1-weighted the high-resolution anatomical MRI template. Areas of significant decreases (left panel) and increases (right panel) in rCBF are mapped separately. Regional abbreviations are defined in Tables 2 and 3.

recovery are generally thought to reflect those detected during the acute episode (Pai and Yang, 1999; Takeuchi et al., 2004), this assumption has yet to be supported conclusively by experimental data. Differences in methods of image analysis, which typically have assessed rCBF in TGA patients within variably defined ROIs, have also likely contributed to the inconsistency in findings across studies. Our use of a voxel-based analysis may have facilitated detection of hemisphere-specific abnormalities in rCBF in the TGA patients, as several of these abnormalities, such as those in Broca's region, may have been too small to detect in ROI-based analyses.

Most blood flow studies performed during or soon after the amnestic episode have demonstrated abnormalities in perfusion of brain regions that subserve memory processes. Whether these perfusion deficits cause TGA (as they might in the presence of ischemia, for example) or whether they simply reflect reductions in the underlying neural activity of those brain structures, with causes for the reduced neural activity residing elsewhere, is unknown (Jovin et al., 2000; Pai and Yang, 1999; Schmidtke et al., 1998; Takeuchi et al., 1998). Our findings do not include disturbances in blood flow to mesial temporal lobe structures that have been reported in prior studies, suggesting that abnormal blood flow to these regions may not be a necessary feature of the pathophysiology of TGA. It is possible, however, that abnormal flow to these structures resolved immediately after the acute onset of amnesia in our sample, prior to scanning. Thus, mesial temporal regions could be involved during the initial phase of the attack, with areas of abnormal perfusion moving from the mesial temporal to temporal-parietal cortices during the early stages of resolution of the most severe anterograde amnesia and confusion. A more likely explanation for our failure to detect disturbances in mesial temporal lobe structures, however, is the imprecision of spatial normalization procedures across individuals and the need to implement large spatial filters that may obscure group differences in perfusion in small brain regions, such as the hippocampus (Peterson, 2003), if perfusion is indeed altered in those regions. Another possible explanation for our failure to detect disturbances in flow in the mesial temporal lobe is the relative insensitivity of blood flow measurements in detecting early ischemia. Consistent with this possibility is a study using diffusion weighted imaging, a more sensitive measure of early ischemia than are blood flow measures, to demonstrate the evolution of ischemic lesions in the hippocampus in a large sample of persons with TGA within the first 48 h of illness (Sedlaczek et al., 2004).

Instead of implicating the hippocampus, our findings suggest that hemisphere-specific abnormalities in rCBF may contribute to the pathophysiology of TGA. In particular, our findings suggest that hemisphere-specific disturbances in blood flow to receptive and expressive language regions may contribute either to the cause of TGA or to compensatory responses in the service of its resolution. Flow to Wernicke's receptive language region was significantly reduced in the left hemisphere, whereas flow to the homologue of Broca's expressive language regions was increased in the right hemisphere in the patient group. That the hemisphere-specific disturbances in flow centered primarily on language regions is perhaps not surprising, given that the strongest evidence for functional lateralization of the CNS is in the language system (Hugdahl, 2000).

Why the hemisphere-specific abnormalities involved decreased flow to receptive language regions in the left hemisphere and increased flow to anterior language regions in the right hemisphere, however, is unclear. Perhaps under-activity of receptive language regions, together with reduced activity of other putative left hemisphere functions—functions such as the processing of local features (Christman, 1993; Hellige, 1993), formation of categorical judgments (Kosslyn, 1987), processing of temporal information (Hutsler and

Galuske, 2003), and the symbolic representation of local features of the environment that are communicated to conspecifics (Hugdahl, 2000)—fundamentally disrupted in persons with TGA the language-based processes that support the formation and consolidation of conscious memories. Under-activity of these left hemisphere functions could induce attempts at compensation by complementary neural systems in the right hemisphere, which include expressive language functions in the frontal lobe and visuospatial systems in the right midtemporal cortex and pulvinar nucleus of the thalamus (Vogel et al., 2003). Similar right hemisphere processes that compensate for deficiencies in functioning of receptive language regions in the left hemisphere have been documented extensively in persons with dyslexia (Pugh et al., 2001). This interpretation of hemisphere-specific abnormalities in blood flow in persons with TGA is of course speculative, although it does lead to the testable hypothesis that detailed neuropsychological testing of components of the language systems in persons with TGA will reveal significant deficits compared with healthy controls, either because receptive language functions within the left hemisphere are disturbed, or because the tests exceed the limited capacity of already-taxed compensatory systems in the right hemisphere. Preliminary experimental support for this hypothesis includes evidence of deficits in verbal fluency (Kessler et al., 2001) and selective deficits in tests of verbal but not spatial memory after resolution of the acute, global amnestic episode in large, independent cohorts of patients with TGA (Hodges and Oxbury, 1990b; Mazzucchi and Parma, 1990).

Alternatively, hemisphere-specific deficits in rCBF could contribute to the pathophysiology of TGA by disrupting hemisphere-specific systems that support the perception of emotional valence, thus reducing the emotional salience of environmental stimuli that facilitate mnemonic encoding and retrieval. Anterior portions of the left cerebral hemisphere are thought to contribute to the perception of positive emotions, and anterior portions of the right hemisphere support the experience of negative emotions (Davidson, 1995; Shenal et al., 2003). Left hemisphere hypofunctionality, reflected in reduced rCBF in our sample, could interfere with positively valenced experiences and thereby increase stress responsivity, perhaps accounting in part for the widely recognized fact that stressful life experiences frequently seem to accompany the onset of the acute amnestic episode in persons with TGA (Fisher, 1982; Inzitari et al., 1997; Pantoni et al., 2000).

Limitations of this study include the absence of detailed neuropsychological assessments, particularly measures of language functioning. Also, the number of TGA patients, though larger than in most prior studies, is still small and may have contributed to false negative findings, particularly in the hippocampus. The accuracy of spatial normalization would have been improved through the simultaneous acquisition of high-resolution MRI scans and the use of extracerebral fiducial markers for coregistration of the SPECT images. Finally, detailed angiography was not performed in any of the patients, and therefore we were unable to exclude underlying vascular causes for the observed hemispheric abnormalities.

Given our findings of hemisphere-specific abnormalities in rCBF and the unique cognitive and emotional functions that each of the cerebral hemispheres is thought to subserve, future studies of TGA should include detailed neuropsychological assessments of receptive and expressive language functions, hemispheric biases for language functioning, local and global processing, symbolic representation, categorical judgments, time perception, and the perception of emotional valence—all of which are thought to represent the functioning of neural systems that are relatively hemisphere-specific. Those neuropsychological assessments should be coupled with quantitative brain imaging studies of cerebral perfusion and more direct measures of neuronal activity, such as electroencephalography and magnetoencephalography, which would be expected to show reduced activity in temporal-parietal portions of the left cerebral hemisphere and markedly altered measures of electrical coherence across hemispheres.

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