Transient global amnesia - acute SPECT functional imaging and neuro-psychological deficits

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The importance of transcranial Doppler ultrasound and HMPAO SPECT in functional imaging of the brain is emphasised.

Abstract

Five patients with transient global amnesia (TGA) were seen clinically and studied neuropsychologically and with SPECT scanning within 24 hours in four and one within 48 hours of the attack. The memory deficits were characteristic of TGA and the magnetic resonance brain scans were normal in all patients. The SPECT scans showed hypoperfusion in the frontal and thalamic regions in all patients. In addition biparietal hypoperfusion was seen in one, parieto occipital in two and unilateral temporal in two patients. Transcranial Doppler studies were performed in three of the five patients and revealed abnormalities of possible relevance in one. Two of the SPECT studies had normalised when repeated at approximately 2 months post ictus. These five patients represent relatively "pure" forms of TGA as they all had normal MRI scans which excluded other disease processes such as subclinical or silent strokes. The frontal hypoperfusion in all five patients is of interest given the role of the frontal lobes in memory processing.

Transient global amnesia (TGA) remains a clinical diagnosis of unknown pathophysiology with no corroborative laboratory or radiological test. Despite over one thousand case reports in the literature,[1-9] neuropsychological assessment at time of or immediately after the ictus is limited to less than a dozen cases.[1,3-5] Strict definition as recommended by the Oxford criteria was not used in the majority of studies.[1] Several functional scanning studies, mainly single photon emission computed tomography (SPECT) reports and one positron emission computed tomography (PET) study, report of thalamic and/or neocortical hypoperfusion with hippocampal, temporal, frontotemporal, thalamus, hemicortical and mesial temporal sites of decreased cerebral blood flow.[3,10-19] Functional imaging with SPECT and PET may be useful in elucidating the cause for the most popular proposed mechanisms which include cerebral ischaemia, seizures and migraine. To date 10 such studies have been published describing 13 patients. In these studies, magnetic resonance imaging (MRI) scans were not reported on, or not performed in six studies and were abnormal in a further two. In the remaining two studies MRI scans were performed 10 days and three

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months post ictus.[3,10-19] This report describes five patients in the acute phase, all with normal MRI scans. To our knowledge, this study represents the largest case series of TGA patients with normal MRI scans but abnormal SPECT scans.

Methods

The five patients were derived from the Durban Stroke Data Bank (DSDB), (n=600) with presumed stroke as the admitting diagnosis. They were evaluated according to the tailored protocol of the DSDB which incorporates a prospective, contemporary stroke investigative evaluation including duplex and transcranial Doppler, MRI or computerised tomography (CT) brain scanning, prothrombotic screens cardiac evaluation including transoesophageal echo, angiography and SPECT scanning where appropriate. Special attention is given to the assessment of higher cortical function deficits (HCFD) with a screening examination. In brief, this encompasses eight major groups of HCFD (aphasias, amnesias, apraxias, agnosias, alexias, neglect syndromes, frontal lobe syndromes and miscellaneous group) with subcategories, all predefined. Focussed neuropsychological testing is performed in those patients with HCFD abnormality.

Clinical

The Oxford definition of TGA was used to define the clinical syndrome (Table I).

Neuropsychological examination was performed by a neuropsychologist in four patients and by the first author in patient 2. In all patients, the focus of the assessment was on memory functioning.

SPECT scanning

Twenty Millicuries 99m Technetium - HMPAO 99 is administered intravenously. Ceretec with Technetium produces a lipophilic complex which crosses the blood brain barrier and is retained in the brain,

Table I: The Oxford TGA study diagnostic criteria for Transient Global Amnesia[1]

Attacks must be witnessed by a capable, reliable observer who was present at time of attack.
Clear cut anterograde amnesia must be present during the attack.
No alteration in consciousness or loss of personal identity may be present.
No focal neurological symptoms or functionally relevant signs may be present.
Epileptic features must be absent.
Attacks must resolve within 24 hours.
People with recent head injury or known active epilepsy are excluded.
Loss of personal identity is a feature of psychogenic or hysterical amnesia. It does not occur in patients with permanent memory loss due to structural brain disease Korsakoffs syndrome no matter how profound the degree of retrograde amnesia.

allowing assessment of regional cerebral blood flow. Imaging commenced 2-3 minutes after the injection of the tracer. The patient is positioned as comfortably as possible with the room slightly darkened and is encouraged to be as relaxed as possible. Scans are obtained for 20 seconds, with regular 6 degree rotation of the camera head around the patient, completing a 360 degree rotation with approximately 60 images obtained. This required cooperation from the patient for a period of about 30-40 minutes. A medium to high resolution collimator was used on the gamma camera. Reconstruction was performed with positioning of the patient in the orbitomeatal line, in the transverse, coronal and saggital planes. Three dimensional reconstruction was also performed. Images were interpreted on the computer screen comparing right and left regions of interest. This was done both visually and semi quantitatively. The transaxial slice with the largest perfusion defect was identified and a circular region of interest traced over that area. These circular regions of interest (ROI) were also obtained for six areas of the grey matter. These included the cerebellum, thalami, basal nuclei, frontal, parieto occipital and temporal regions. These areas and their mirror images on the homologous region of the other hemisphere were stored on a template and adjusted when required for a particular scan. The ROI radioactive counts were compared to the mean count of the two cerebellar hemispheres and expressed as a percentage of the mean cerebellar count according to the formula (1 - ROI/mean cerebellar count).

Transcranial Doppler

The basal cerebral vessels and all major branches of the circle of Willis were insonated via the temporal and sub occipital windows with the EME-Transcan transcranial Doppler using mounted 2 MHz probes. Flow velocities and pulsatility indices (Gosling) were measured with special attention to the identification of intracranial stenoses and emboli detection (15 minutes monitoring).

Case reports

Patient 1

An alert, attentive 57 year old woman brought to hospital by her husband with complaints of not remembering and repeating herself since 11h00 one morning. A sudden onset of occipital pain was reported by her husband which the patient no longer remembered. During the initial clinical encounter it became apparent that her memory was defective until the prior evening. Stroke risk factors included significant smoking and previous mild hyperlipidaemia. The medical history was otherwise unremarkable. Clinical neurological examination with specific attention to aphasias, apraxias, agnosias, neglect syndromes, alexias and frontal lobe function was normal. Defective short term memory as tested by digit span and 5 minute recall was noted. The Boston Naming Test score

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was 50/60. Routine stroke investigations including blood counts, lipogram, glucose, erythrocyte sedimentation rate, electrolytes electrocardiogram and chest radiograph were normal.

A neuropsychological assessment was performed within 5 hours of the attack.

The tests administered included the Wechsler Memory Scale, Rey's Auditory Verbal Learning Test, Rey's Complex Figure Test, South African Wechsler Adult Intelligence Scale, Trail Making Test and Symbol Digit Modalities Test. Abnormalities detected by these tests are noted in Table II.

Neuroradiological investigations

T1 and T2 weighted MRI brain scanning was performed 12 hours after the onset and was normal. Transcranial Doppler sonography revealed abnormally low basilar artery velocity of 10-18 cms/sec. SPECT brain scanning approximately 10 hours after presentation,

Table II: Neuropsychological and SPECT findings

	Orientation	Immediate memory	Anterograde amnesia	Retrograde amnesia	Executive skills	Language skills	SPECT scan	ROI cerebello-cortical % Difference- R	ROI cerebello-cortical % Difference - L
Patient 1	Orientated	Intact	Verbal and nonverbal memory: quantity of information recalled impaired. Significant shrinkage after interference. Poor recognition memory which points to retention problem.	Patchy for about one week prior to the event	Approach to tests unplanned and cavalier; inattention to detail. Failure to self monitor and correct errors. Difficulty inhibiting irrelevant associations and releasing from proactive interference.	Normal	Bifrontal L>R, Bithalamic and biparietal hypoperfusion	48 38 29	63 34 26
Patient 2	Normal	Intact	Verbal memory; quantity of information recalled impaired. Visual memory impaired.	Personal semantic memory intact. Recall of auto-biographical episodes defective. General semantic memory of recent origin impaired.	Normal to clinical bedside testing (FAS test and Rey Figure)	Confrontation naming impaired; in particular with respect to animals	Bilateral frontal, thalamic and parietoccipital hypoperfusion	44 64 49	48 65 60
Patient 3	Disorientation for date and place. Orientated for time and person.	Intact	Verbal memory; quantity of meaningful and non meaningful information recalled impaired. Significant shrinkage after interference. Poor recognition memory which points to retention problem. Visual memory; mildly impaired.	Personal semantic memory intact. Recall of recent autobiographical episodes impaired. General semantic memory of recent origin impaired (eg famous faces).	Approach to tasks unplanned and poorly organised. Failure to self monitor and correct errors.	Intact	Bilateral frontal, thalamic and temporal hypoperfusion	45 60 59	28 46 53
Patient 4	Disorientated for time	Intact	Verbal memory; quantity of information recalled impaired. Visual memory; not assessed.	Recall of recent autobiographical data episodes impaired.	Not assessed formally but decreased self awareness evident as unconcerned about slovenly appearance and had become docile - behaviours consistent with frontal lobe dysfunction	Intact	Bilateral frontal, thalamic and right temporal hypoperfusion	44 37 28	36 33 62
Patient 5	Orientated for time, date, place and person	Intact	Verbal memory; quantity of non meaningful and meaningful information recalled impaired. Significant shrinkage after interference. Good recognition memory which points to retrieval problem. Visual memory; immediate recall intact but delayed recall borderline range.	Personal semantic memory intact. Recall of auto-biographical episodes from early adulthood and recent past impaired. General semantic memory mildly impaired (eg recognition of famous faces).	Approach to complex novel tasks poorly planned and organised	Verbal fluency mildly impaired	Bilateral frontal thalamic and left parieto occipital hypoperfusion	61 41	41 39

Abbreviations: ROI - regions of interest
L - left; R - right

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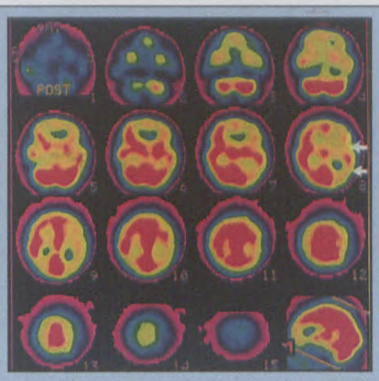

Figure 1: SPECT scan of patient 5 - Visual analysis: Transaxial section indicating hypoperfusion of left frontal, parietal and thalamic regions (arrows).

revealed visually appreciated perfusion defects in the left frontal, superior right parietal and left parietal regions (Figure 1). The percentage decrease of ROI greater than 15% with respect to the mean cerebellar count is noted in Table II. Follow up 2 months post ictus revealed normal neurological and focussed neuropsychological testing, normal transcranial Doppler insonation of the basilar artery and the SPECT brain scan showed normal perfusion bilaterally.

Patient 2

A financial advisor aged 53 years awoke normally one Sunday morning, read the newspapers with his wife, had sexual intercourse and immediately thereafter kept repeating himself and could not remember details of the preceding day. Some events over the preceding week were also defective according to his wife. Within three and a half hours he had recovered back to normal as judged by himself and his wife. Stroke risk factors were not present apart from personal stress and an occasional moderate alcohol intake. His past medical history was unremarkable. He was seen within 3 hours of the attack. The neurological examination was normal and neuropsychological examination performed. Routine stroke investigations including blood counts, lipogram, glucose, erythrocyte sedimentation rate, electrolytes electrocardiogram and chest radiograph were normal.

The screening neuropsychological assessment comprised a clinical memory evaluation and the Boston Naming Test. The assessment findings are detailed in Table II. Formal testing for aphasias, apraxias, agnosias, neglect syndromes, alexias and frontal lobe function were normal. The tests administered included orientation - normal for date, time, place, person, the Rey Osterreith Complex Figure Test, Modified Famous Faces Test (last 6 US Presidents), Digit span at 5 minutes, Three Words/Three Shapes Test, confrontation naming (Boston Naming Test) and FAS Test. The abnormalities detected are summarised in Table II.

Neuroradiological investigations

The T1 and T2 weighted MRI brain scan performed approximately 24 hours after the event was normal. Transcranial Doppler 4 hours after the onset showed was notable for non insonation of the right posterior cerebral artery. The left posterior cerebral artery was easily insonated and the basilar artery flow normal. SPECT scanning was performed within 12 hours and revealed a visually appreciated left parieto-occipital perfusion defect. The percentage decrease of ROI greater than 15% with respect to the mean cerebellar count is noted in Table II. Follow up 2 months post ictus revealed a persistent animal specific naming defect but this had improved. The transcranial Doppler and SPECT brain scan were repeated at this time and were both normal.

Patient 3

A 54 year old woman awoke one morning unable to remember either the month or year or why she was at the place they were on holiday. She could recite accurately her home address and personal names. Repetitive questioning as to what she and her husband were doing at the holiday venue followed for the next few hours. No stroke risk factors were present and her relevant past medical history was otherwise unremarkable. Examination, both systemic and neurological was normal. Bedside autobiographical review made it clear that her memory defect stretched back several weeks prior to the ictus. Routine stroke investigations including blood counts, lipogram, glucose, erythrocyte sedimentation rate, electrolytes electrocardiogram and chest radiograph were normal. She normalised clinically over a 12 hour period.

Neuropsychological evaluation was performed within 6 hours. The neuropsychological tests administered were the Wechsler Memory Scale, Rey's Auditory Verbal Learning Test, Luria's Neuropsychological Investigation expanded by the second author to include autobiographical and general semantic memory and a Famous Faces Test. Overall she presented preservation of immediate memory, anterograde amnesia for both verbal and nonverbal material and retrograde amnesia characterised by a difficulty in recalling autobiographical episodes. Her orientation and immediate memory was normal as tested by the Digit Span Task. Anterograde deficits for verbal memory was severely impaired and displayed a typical lowered and fluctuating plateau associated with frontal lobe impairment. Recognition memory was poor and recall of information during assessment was intermixed with word repetitions. Recall of material presented in context was severely impaired. Visual memory was mildly impaired. The neuropsychological assessment findings are noted in Table II.

Neuroradiological investigations

CT and MRI (T1 and T2) brain scans and duplex and transcranial sonography were all normal. SPECT scanning done within 12 hours of the ictus revealed visually appreciated hypoperfusion defects in the left frontal and parietal regions. The percentage decrease of ROI greater than 15% with respect to the mean cerebellar count is noted in Table II.

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Patient 4

A 62 year old overweight retired accountant was free diving in the surf zone for crayfish with his son one day. When he surfaced he was behaving strangely in that he was unable to recall recent events and was concerned about not having their crayfish licence that they had recently acquired. His son had noticed that he had spent an abnormally long time in a pool amongst rocks that does not normally have crayfish. He tied a handkerchief around his head and seemed to have a headache. Thereafter he kept rambling about the past and repeating himself. On arriving home, he stood looking bemused at items that he himself had packed on a car trailer the day before and asked family members what these were doing there. Current items on his workbench that he was busy with the day before also puzzled him. He was taken to the doctor still in his gear used for diving which he did not wish to change out of first. This was most unlike him as he was normally fastidious about his appearance. He had also become very docile and agreed to everything which was also unusual for him. Repetitive questioning was ongoing. His only relevant past history and stroke risk factors were hypertension on treatment with Captopril and Aspirin and attacks of gout in the past. General and neurological examination was normal apart from a blood pressure initially of 220/115 subsequently reduced to 175/100. He normalised with respect to the above deficits within approximately 6 hours. Routine stroke investigations including blood counts, lipogram, glucose, erythrocyte sedimentation rate, electrolytes electrocardiogram and chest radiograph were normal.

A clinical bedside neuropsychological assessment with a focus on memory evaluation was performed within 5 hours of the episode. Tests administered included the Rey Osterreith Complex Figure Test, Modified Famous Faces Test (last 6 US Presidents), Digit span at 5 minutes, Three Words/Three Shapes Test, confrontation naming (Boston Naming Test) and FAS Test. The abnormalities detected are summarised in Table II.

Neuroradiological investigations

The MRI brain scan and duplex Doppler sonography of his cervicocephalic vessels were normal. The SPECT scan performed 24 hours after presentation revealed to visual inspection a marked right hemisphere hypoperfusion including the right frontal lobe and the right thalamic region. The percentage decrease of ROI greater than 15% with respect to the mean cerebellar count is noted in Table II.

Patient 5

A 48 year old man suddenly questioned the type of shirt he was wearing while sitting on the edge of his bed one morning soon after wakening. The details were derived from his wife as he did not recollect anything about the event. He kept asking where he was, did not know that he had bought a new car 2 weeks previously. He asked about the shirt he was wearing at least 4 times and kept blinking his eyes, asked about the day of the week, where he was, asked questions about the rugby magazines next to his bed that he had just been reading. His wife recalled him touching his forehead and saying he had a "funny headache". The repetitive questioning lasted for about 20 minutes but for the rest of the day he seemed to be "floating and not with it" and he felt "fuzzy". He was in a very stressful situation at the time, setting up his own business venture which was not going according to plan. Two weeks prior to the event he was away for the weekend with his wife and recalled details accurately according to his wife. His past history was unremarkable with no previous illness or surgery and no cerebrovascular risk factors. He was seen clinically within 24 hours of the attack and general and neurological examination was normal. Routine stroke investigations including blood counts, lipogram, glucose, erythrocyte sedimentation rate, electrolytes electrocardiogram and chest radiograph were normal.

Neuropsychological testing was performed within 48 hours and tests included the Rey Osterreith Complex Figure, Trail Making Test, Digit Span Test, Rey Auditory Verbal Learning Test, Wechsler Memory Scale, Logical Memory Task, FAS Test, Famous Faces Task, Category Naming Test, Autobiographical Incidents Schedule and selected tasks from Luria's Neuropsychological Investigation.

Neuroradiological investigations

The MRI brain scan and duplex Doppler sonography of his cervicocephalic vessels were normal. The SPECT scan performed 48 hours after presentation revealed marked visually appreciated left hemisphere hypoperfusion, including the left frontal lobe and hypoperfusion of both thalamic regions. The percentage decrease of ROI greater than 15% with respect to the mean cerebellar count is noted in Table II.

Discussion

The five patients described are unique in that they presented with classical features of TGA as required by the Oxford TGA study diagnostic criteria, had normal MRI scans and abnormal SPECT scans in the acute stage. The SPECT scans and neuropsychological testing were performed within 24 hours of onset of the first symptoms in 4 patients and within 48 hours in one. Neuropsychological assessment was consistent with TGA in which the pervasiveness of anterograde and retrograde amnestic dysfunction is rapid in onset and in striking contrast to the preservation of immediate memory and the relative sparing of other higher mental functions. The

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dysexecutive findings in patients 1, 3 and 5, mildly impaired verbal fluency in patient 5 and behavioural abnormalities in patient 4 are consistent with a mild frontal disturbance. The SPECT scans of these 5 patients revealed frontal hypoperfusion as part of the SPECT abnormalities.

MRI brain scanning is the most sensitive anatomical scan to exclude small infarcts and might be regarded as a prerequisite to exclude small or previously clinically silent infarcts in such patients. TGA remains a clinical diagnosis and one of the requirements is the absence of other neurological deficits. MRI scanning is an accurate method to exclude subclinical deficits in this setting. If sensitive paraclinical and radiological testing is also normal, as in these five cases, a purer form of TGA presentation may be studied.

Table III: Sites of hypoperfusion in the acute stage of TGA as noted by functional scanning (SPECT and PET) in studies to date[3,10-19]

Region	Side
Hippocampal	Bilateral
Temporal or frontotemporal	Right and left
Temporal and frontal	Bilateral
Temporal	Left
Frontal	Right and left
Thalamus and whole cortex	Bilateral
Mesial temporal	Bilateral
Hippocampal and amygdala area	Left
Mesial temporal and thalamus	Left

The studies performed to date using PET[10,18] or SPECT[3,11-17] and 133 Xenon[19], have indicated a variety of sites with perfusion defects, both bilateral and unilateral, in the acute stage of TGA - Table III. The patients under discussion, with perfusion deficits noted both frontal and thalamic regions in all patients, the parieto occipital regions in 2 and unilateral temporal regions in 2, is to our knowledge, the largest case series of functional scanning in acute TGA together with normal MRI brain scans. Although a variety of lesions, including cerebral infarcts and haemorrhages have been reported in the temporal lobes and more commonly the thalami on CT brain scans[20-22] of TGA patients, it may be argued that such cases no longer represent pure forms of TGA. In these cases, a transient neurological deficit may have been present very briefly at the onset of ictus with brain scan paraclinical evidence of a vascular lesion akin to the events described as CITS (cerebral infarcts with transient symptoms).

The perfusion deficit might reflect a diaschisis effect of primarily thalamic dysfunction or neocortical in origin. In the study of Ott *et al* of unilateral amnesic stroke[23], a particular vulnerability for TGA was postulated with dysfunction in the left amygdalohippocampus or diencephalon. Whatever the mechanism, a primary diencephalic insult seems plausible based on clinical and functional scanning data. All five of our cases showed relative thalamic hypoperfusion. With regard to the aetiology of TGA, the normal MRI scans performed within 24 hours of onset argue against a cerebral infarct and subclinical brain damage. A recently proposed hypothesis posits that cerebral hypoperfusion may be secondary to a neuronal hypometabolism itself initiated by excitotoxic neurotransmitter release temporarily impairing memory function.[1] The finding of the SPECT hypoperfusion in neocortical regions is consistent with such an hypothesis, the normal MRI scans marshalling evidence against cerebral ischaemia as the primary mechanism. A recent positron emission computed tomography study in acute TGA demonstrated matched flow metabolism depression more consistent with neuronal dysfunction such as due to a seizural or migraine spreading depression mechanism.[10]

Certain neuropsychological findings are worthy of further comment. The dysexecutive findings in patients 1, 3 and 5 and probably also patient 4, are consistent with a disruption in the organisation and control of the learning, retention and retrieval process highlighted by Baron *et al.*[10] The confrontation naming difficulty in patient 2 has also been noted by Kritchevsky *et al.*[24] The SPECT scan revealed a left parietal perfusion deficit which may be the basis of this problem. In patients 3 and 5 visual memory was not as severely affected as verbal memory. A similar finding has been made by Walsh[25] in some of his cases. Patient 5 was assessed 48 hours post TGA onset and in this case the discrepancy may reflect the earlier recovery of non verbal memory described by Okado *et al*[26] in their two cases. The neuropsychological assessment findings would seem to support this in that although the main features of TGA were the same in all five patients, there were individual differences in the severity and nature in which the symptoms manifested in each case. Constraints on neuropsychological assessment include the rapid onset and brevity of attack. Distress and frequently marked repetitive questioning frequently preclude a lengthy wide ranging neuropsychological assessment.

Our study reports on individuals free of cerebrovascular disease with minor risk factors, no previous illness of note, neocortical hypoperfusion with no evidence for a stroke mechanism on MRI scanning. Recent studies with relatively large numbers of TGA patients argued strongly against a thromboembolic aetiology of TGA.[27] The transcranial Doppler (TCD) of low velocity in the basilar artery in case 1 may have reflected a cerebral hypometabolism. In case 2, the finding of an absent signal from the left posterior cerebral artery and low basilar artery velocity with subsequent normalisation are

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consistent with posterior circulation embolic mechanism residua. The TCD findings, though interesting do not permit conclusions, as the findings are nonspecific.

SPECT scanning does not permit pathophysiological conclusions as a distinction between flow reduction caused by cerebrovascular disease or flow reduction due to neuronal dysfunction cannot be made. Cortical flow reduction secondary to thalamic diaschisis itself due to a posterior circulation ischaemia is a possible explanation. The 5 patients represent relatively pure TGA cases both clinically and on investigation with varying cortical hypoperfusion on SPECT scanning which normalised at one month follow up in 2.

TGA may be a core syndrome with several sites of dysfunction within the neuronal network subserving memory possible.[10] In addition, support for a neuronal dysfunction rather than vascular mechanism, possibly thalamic based with secondary and transient cortical hypoperfusion seems most plausible in the cases described. This was first suggested by Trillet in 1987 using Xenon inhalation in TGA.[19] The case series described, gives support to such an hypothesis because of the normal MRI scans in all five patients with its proven sensitivity for detecting cerebral infarction. The transient relatively mild frontal lobe disturbance noted in 4 of the 5 patients hints at a secondary disturbance such as that seen with diaschisis. Recent neuropsychological, PET and functional MRI data[28-31] provide strong support for the prefrontal cortex in human working memory. Activation of this area has been noted in cognitive tasks that are thought to be involved in declarative episodic or working memory.[28] The frontal hypoperfusion in our 5 patients is consistent with such findings and also supports the theory of Baron *et al*[10] of a prefrontal metabolic depression, itself secondary due to thalamic dysfunction.

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Addendum:

Posterior circulation positional transient ischaemic attacks due to persistent hypoglossal artery redundancy
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