doi:10.1093/brain/awp133 Brain 2009: 132; 1882–1888 | 1882

BRAIN
A JOURNAL OF NEUROLOGY

Reduced medial temporal lobe functionality in stroke patients: a functional magnetic resonance imaging study

Liselore Snaphaan,[1] Mark Rijpkema,[2] Inge van Uden,[1] Guillén Fernández[1,2] and Frank-Erik de Leeuw[1]

1 Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Centre for Neuroscience, Medical Centre, Radboud University Nijmegen, The Netherlands
2 Radboud University Nijmegen, Donders Institute for Brain, Cognition and Behaviour, Centre for Cognitive Neuroimaging, Radboud University Nijmegen, The Netherlands

Correspondence to: Frank-Erik de Leeuw,
Department of Neurology,
Radboud University Nijmegen,
Medical Centre, PO Box 9101,
6500 HB Nijmegen (HP 935),
The Netherlands
E-mail: H.deLeeuw@neuro.umcn.nl

Stroke is a leading cause of disability, not only because of motor limitations, but also because of the frequent occurrence of post-stroke cognitive impairment. This is illustrated by the fact that the risk of post-stroke dementia is reportedly higher than a recurrent stroke. The loss of subcortical and cortical functions in the post-stroke cognitive dysfunction spectrum is usually well explained by the size and location of the infarction. However, this does not apply for post-stroke memory dysfunction (especially episodic memory dysfunction), as there is almost never an infarction in the medial temporal lobe. Involvement of the medial temporal lobe in post-stroke memory dysfunction seems likely since this structure is essential for memory encoding and retrieval. For a proper episodic memory function, the medial temporal lobe depends on intact connections with virtually the whole brain. Disconnection from other brain areas due to the infarction could lead to a reduced medial temporal lobe function and the attendant reduced episodic memory function. We investigated medial temporal lobe functionality in 28 'first-ever' stroke patients and 22 healthy controls with the aid of functional magnetic resonance imaging. Stroke patients with a reduced episodic memory function 6–8 weeks after infarction had reduced medial temporal lobe functionality. Post-stroke reduced medial temporal lobe functionality may be responsible for the frequent observation of impaired post-stroke episodic memory function. Insight into this mechanism could be helpful in identifying which stroke patients may be at increased risk for developing post-stroke dementia and those who could benefit from early cognitive rehabilitation.

Keywords: stroke; fMRI; MTL; imaging; *n*-back task

Abbreviations: fMRI = functional magnetic resonance imaging; MMSE = mini mental state examination; MTL = medial temporal lobe; NIHSS = National Institute of Health Stroke Scale

Introduction

Stroke is a devastating disease that affects millions of people world-wide every year. It is a leading cause of disability; in the acute phase this is predominantly determined by limitations of motor function that usually show a fairly good tendency to recover in the first weeks, whereas in the subacute and chronic phase post-stroke cognitive impairment is an important

Received June 25, 2008. Revised April 19, 2009. Accepted April 22, 2009. Advance Access publication May 29, 2009

determinant of recovery (Hofgren *et al*., 2007). Cognitive impairment within the first month after stroke affects up to 10%–82% (Rasquin *et al*., 2004) of stroke survivors that surprisingly often goes unnoticed by treating physicians, usually due to a lack of a standardized assessment. The importance of post-stroke cognitive function as a major determinant of post-stroke 'activity-of-daily-life' is illustrated by the fact that the risk of dementia after a stroke is reportedly higher than the risk of a recurrent stroke (Yokota *et al*., 2004).

Most of the spectrum of post-stroke cognitive dysfunction is usually well explained by the size and location of the infarction, whereas an explanation of the occurrence of memory dysfunction after stroke (especially episodic memory dysfunction) is currently lacking, as there is almost never an infarction in the medial temporal lobe (MTL) (Snaphaan and de Leeuw, 2007). Despite the absence of direct ischaemic structural damage of the MTL, an impaired post-stroke function of the MTL may play a role in the development of episodic memory dysfunction after stroke, as a proper MTL function is essential for memory encoding and retrieval (Brierley *et al*., 2002). After all, for an optimal episodic memory function the MTL depends on intact connections with virtually the whole brain (Suzuki, 2007). Disconnection from these other brain areas due to the infarction could lead to a reduced MTL function, in addition to a reduced episodic memory function. Therefore, we hypothesized that the reduced episodic memory functionality found in stroke survivors is related to a reduced MTL function.

The *n*-back task activates a so-called working memory network that consists of bilateral prefrontal cortex, parietal cortex, thalamus, anterior cingulate and bilateral cerebellum (Callicott *et al*. 1999, 2000). In addition to these working memory-related activations, medial temporal deactivations were also observed with the *n*-back task (Egan *et al*., 2003). Previous studies showed that this deactivation can be used as a marker of MTL functionality (Weinberger *et al*., 1996; Meyer-Lindenberg *et al*., 2001; Egan *et al*., 2003). The *n*-back task is a relatively simple task that can equally well be executed by patients with impaired episodic memory performance and controls, thereby excluding the possibility that differences in test performance (i.e. *n*-back task) can explain differences in MTL activation. Consequently, the *n*-back task is used to assess functionality of the MTL in this study, but it is not a measure of episodic memory performance. We investigated MTL activation by fMRI using the *n*-back task in 28 consecutive 'first-ever' supratentorial stroke survivors and 22 healthy controls.

Study Population and Methods

Patients

Patients were eligible for inclusion if they had an acute symptomatic 'first-ever' supratentorial cerebral infarction between September 2005 and May 2007, and were admitted to the Department of Neurology of the Radboud University Nijmegen Medical Center. The diagnosis of stroke was based on both the presence of acute neurological symptoms that could only be explained by vascular lesion in a specific vascular territory and a compatible lesion on CT or MRI scan. Patients were excluded on the basis of the following criteria: age >75 years, pre-existent cognitive decline [considered present when the patient had a score of <78 on the short Informant Questionnaire on cognitive decline in elderly (IQCODE) (de Jonghe *et al*., 1997)] or concurrent cognitive impairment [considered present when the patient had a score of ⩽23 on the Mini Mental State Examination (MMSE) (Folstein *et al*., 1973)], history of concomitant neurological disease, presence of diseases or the use of medications that were likely to affect cognition, history of alcohol or drug abuse, severe white matter lesions [operationalized as a score ⩾2 in two or more regions as assessed by the Age-Related White Matter Changes scale (Wahlund *et al*., 2001)], clinical or radiological evidence of a previous infarction, aphasia and MRI contra-indications (metal implants, pacemaker and claustrophobia). In total 52 patients fulfilled the criteria; 38 of them agreed to participate in the study (response 73%). There were no differences between responders and non-responders with respect to the baseline characteristics described in Table 1. Ten were left out of the analysis because of distortion of MRI data by movements ($n=3$), lack of adherence to task instructions ($n=2$) or early break-off during scanning (anxiety, $n=5$), which resulted in a study population of 28 patients.

Controls

Healthy control subjects ($n=29$) were recruited from the general population through advertising. They were closely matched to the patient group with respect to age, gender and education. Both patients and controls underwent an identical neuropsychological examination. Seven controls were left out of the analysis because of the presence of silent brain infarcts ($n=4$) or pre-existent cognitive decline ($n=3$).

The medical ethics committee (CMO Arnhem-Nijmegen, The Netherlands) approved the study protocol. All subjects gave written informed consent to participate in this study and only travel costs were reimbursed.

Table 1 Baseline characteristics

	Patients ($n=28$)	Controls ($n=22$)
Age in years (SD)[a]	53.7 (12.6)	51.5 (12.9)
Male%[b]	57.1	50.0
Education (range)[c]	5 (0–7)	5 (2–7)
Right handed (%)[b]	85.7	81.8
Left sided infarction (%)	46.4	
Total brain volume (SD)[a]	1159 (129.3)[d]	1143 (122.9)[e]
Grey matter volume (SD)[f]	661 (67.9)[d]	659 (77.1)[e]
White matter volume (SD)[f]	498 (68.6)[d]	484 (58.5)[e]
Hippocampal volume (SD)[f]	7.1 (1.0)	6.7 (0.9)

Values represent means (SD), median (range), proportions (%) or ml (volume), empty cells indicate no assessment.
Score 5 means 10–11 years of education. No significant differences were found between patients and controls for all these baseline characteristics ($P<0.05$).
a Univariate Analysis
b Chi-square Analysis.
c Mann–Whitney U-analysis.
d Data available for $n=27$.
e Data available for $n=21$.
f Corrected for total brain volume.

Episodic memory assessment

All patients underwent a complete, standardized neuropsychological examination between 6 and 8 weeks after their qualifying stroke covering all cognitive domains, including assessment of mood. Episodic memory was assessed with the California Verbal Learning Task, Dutch version (Delis, 1987). We were particularly interested in the delayed-recall because this measure is most sensitive to MTL function (Mungas *et al*., 1985; Hermann *et al*., 1987). Other relevant tests for the purpose of this particular study included; global cognition (MMSE) and anxiety and depressive symptoms [Hospital Anxiety Depression Scale (Zigmond and Snaith, 1983)]. In addition, educational level was assessed in all subjects using the Dutch classification system (Verhage, 1964), ranging in ascending order from 0 (less than primary school) to 7 (university degree).

Other covariates

Clinical stroke severity at admission was assessed with the National Institute of Health Stroke Scale (NIHSS) (Brott *et al*., 1989). Infarcts were classified according to location by an experienced stroke neurologist (FEdL) according to a standard procedure using neuroimaging (either CT or MRI) at which the symptomatic lesion was best visible. We also assessed the post-stroke functional status 6–8 weeks after stroke by the Barthel Index (Mahoney and Barthel, 1965); ranging from 0 (completely dependent) to 20 (completely independent), and degree of handicap (modified Rankin Scale) (van Swieten *et al*., 1988); ranging from 0 (no symptoms) to 5 (severe disability).

fMRI task design

Patients were scanned 9–12 weeks after the stroke. As a fMRI task design we used a number variant version of the *n*-back working memory paradigm (Gevins and Cuttilo, 1993). The *n*-back task is a paradigm, which activates a so-called working memory network that consists of bilateral prefrontal cortex, parietal cortex, anterior cingulate and bilateral cerebellum (Callicott *et al*., 1999, 2000), whereas MTL deactivation is also observed (Callicott *et al*., 2000; Meyer-Lindenberg *et al*., 2001). In this study an *n*-back task was used with a sequence of 0-back (minimal working memory load) and 2-back conditions (moderate working memory load) arranged in a blocked design.

In the scanner, subjects viewed single digits (Digits 1–9) in white arial font on a black background on a screen in pseudo-random order. Each digit appeared 0.6 s, after which the subjects had to react within 1.5 s by pressing the response button for the target digit. The two conditions (0-back and 2-back) were applied in alternating blocks of 15 digits. The whole experiment consisted of 10 cycles, and thus each subject had to respond to 300 digits. The task took ~12 min and 19 s, in which 308 whole-brain images were recorded. In the 0-back task subjects had to respond to target digit '1'. The 2-back task required the subject to press the response button when a digit occurred which matched the one presented two digits before. Both conditions contained 15% target digits. Subjects were instructed in detail with task examples on a computer outside the scanner until they understood the task procedure. During the experiment subjects were reminded of the actual condition by continuous presentation of the following symbols on the screen: '—' indicated the 0-back condition and '←' indicated the 2-back condition.

Data acquisition

MR data were acquired with a 1.5T Siemens (Erlangen, Germany) Sonata MR scanner, equipped with a circularly polarized head coil. One run of T_2*-weighted blood oxygenation level-dependent images was acquired using echo-planar imaging with each image volume consisting of 35 axial slices [voxelsize 3 mm × 3.5 mm × 3.5 mm; repetition time (TR), 2.40 s; echo time (TE), 30 ms; 64 × 64 matrix; field-of-view (FOV), 224 mm × 224; flip angle, 90°]. After the functional run, a high-resolution T_1-weighted structural MR image was acquired for co-registration and spatial normalization procedures [3D MP-RAGE (magnetization-prepared rapid gradient-echo); TR, 2.25 s; TE, 3.68 ms; 176 contiguous 1 mm slices; 256 × 256 matrix; FOV, 256 mm].

Total brain volume was calculated as the sum of the volumes of grey matter and white matter, which were assessed by automated segmentation of high-resolution T_1-weighted structural MR images using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). All segmented volumes were visually checked using MRIcron (http://www.sph.sc.edu/comd/rorden/mricron/).

Hippocampal volume was assessed by manual segmentation using the interactive software program 'ITK-SNAP' (http://www.itksnap.org) according to a standardized protocol (Brierley *et al*., 2002; Geuze *et al*., 2005) with a high interrater agreement (intraclass correlation coefficient for the left and right hippocampus of 97% and 96%, respectively). Hippocampal volumes were adjusted for total brain volume. This segmentation was done without prior knowledge of both performances on memory tasks and degree of MTL activation during the fMRI experiment.

Data analysis

The first three echo-planar image volumes were discarded to allow for T_1 equilibration. Data were analysed in MATLAB 7.1 (http://www.mathworks.com) using the statistical parametric mapping software SPM5 with the following pre-processing steps: spatial realigning to correct subject motion (none of the subjects exceeded 3 mm motion), co-registration to the mean of functional images using mutual information optimization, slice time correction, spatial normalization to the Montreal Neurological Institute (MNI) T_1 template and spatial smoothing with a Gaussian kernel of 8 mm full-width at half-maximum.

A general linear model (Friston *et al*., 1995) was used to analyze the data. Regressors for the 0-back and 2-back task were convolved with the canonical hemodynamic response function (HRF). To adjust for movement-related activation, the realignment parameters were also added to the model as regressors. The data were high pass-filtered (128 s) to account for low-frequency effects. Contrast images were created for each subject summarizing the differences between conditions (0-back minus 2-back, and 2-back minus 0-back contrast). The single-subject contrast images were entered into second-level random-effects analysis. Group level SPM (t) maps were thresholded at $P = 0.001$ (uncorrected) and the cluster-size statistics FWE (Familywise Error) corrected were used as the test statistics. Only clusters at P (FWE) $\leqslant 0.05$ were considered significant. As we had an *a priori* hypothesis about the MTL (reduced MTL functionality is linked to impaired episodic memory function after stroke), a small volume correction was used for the MTL (Worsley *et al*., 1996). For this purpose,

the MTL region-of-interest from the SPM anatomy toolbox (version 1.5 S. Eickhoff, Institute for Medicine, Research Center Jülich) was used. A two-sample *t*-test was applied to investigate the differences in brain activity between patients and control group during the 0-back minus 2-back contrast and 2-back minus 0-back contrast.

Baseline and clinical characteristics were analysed using SPSS version 14.0. Two-sample *t*-tests were used for between group comparison for continuous data, Chi-square tests for nominal data and Mann–Whitney U-analyses were used for non-parametric data. All effects were tested at the $P < 0.05$ level (two-tailed).

Results

Subjects' characteristics

The study population consisted of 50 subjects with a mean age of 54.2 years (SD 12.8), 46% of them were female, median educational level was 5 and 84% were right-handed. Baseline characteristics of both patients and controls are presented in Table 1. No significant differences were found for age, gender, education and handedness between patients and controls. Total brain volume, grey matter volume, white matter volume and hippocampal volume did not significantly differ between patients and controls.

Clinical and behavioural characteristics of patients and controls are presented in Table 2. There were no differences between patients with a left or right-sided stroke. There were nine patients who had an infarction in the internal capsule (six left; three right), five in the corona radiata (four right; one left), three in the thalamus (one right; two left), four in the occipital lobe (two right; two left), four in the brainstem and three in the parietal lobe (two right; one left).

Table 2 Clinical and behavioural characteristics of participants

	Patients ($n = 28$)	Controls ($n = 22$)
MMSE (SD)[a]	28.1 (1.7)[b]	29.4 (0.8)[c]
Delayed recall words (SD)[a]	9.2 (4.6)	12.4 (2.0)[e]
Anxiety (range)[a]	5.5 (0–12)[d]	4.5 (0–14)
Depressive symptoms (range)[d]	4.0 (0–17)[d]	2.5 (0–14)
Modified Barthel Index (SD)	20 (0.0)[d]	20 (0.0)
Modified Rankin scale (range)	1 (0–3)[d]	
NIHSS score (range)	2 (0–16)[e]	
Correct responses on *n*-back task (%)		
0-back condition mean (SD)[a]	99.1 (2.3)	99.7 (0.7)
2-back condition mean (SD)[a]	93.3 (4.7)	94.9 (2.8)

Values represent means (SD), median (range) or proportions (%), empty cells indicate no assessment.
a Univariate Analysis.
b Data available for $n = 27$.
c Significant differences between patients and controls ($P < 0.05$).
d Data available for $n = 26$.
e Data available for $n = 25$.

Patients performed significantly worse [mean words 9.2 (SD 4.6)] than controls [mean words 12.4 (SD 2.0)] on the delayed recall task of the California Verbal Learning Task ($P = 0.004$). There was no difference between other clinical and behavioural characteristics, except for the MMSE score. Despite the difference in episodic memory function, patients and controls did not perform significantly different on the *n*-back task in the scanner.

fMRI responses

Patients and controls

In the 0-back minus 2-back contrast brain activation was observed bilaterally in the frontal lobe, MTL, cingulate gyrus, insula, occipital lobe and cerebellum (Fig. 1A). In the 2-back minus 0-back contrast brain activation was observed bilaterally in the frontal lobe, brainstem (pons), cerebellum and temporal lobe (Fig. 1B). These two activation patterns (Fig. 1A and B) correspond with brain areas typically activated by the *n*-back paradigm (Callicott *et al.*, 1999, 2000; Meyer-Lindenberg *et al.*, 2001). These activation patterns were similar for patients and controls.

Furthermore, we found a positive correlation between MTL activation (in the 0-back minus 2-back contrast) and performances on the California Verbal Learning Task in controls ($\beta = 0.48$, $P = 0.02$), but not in patients.

Patients versus controls

Exploratory whole-brain analysis revealed no significant differences [P (FWE) > 0.05] between stroke patients and controls, probably due to limited power as the study was designed to look exclusively at MTL functionality in a heterogenous group of stroke patients.

As we wanted to compare MTL functionality (assessed with the *n*-back task) between patients and healthy controls, we subsequently focused specifically on the MTL. Both patients and controls showed MTL activation during the 0-back minus 2-back contrast, however patients showed significantly less left-sided MTL activation [$x = -18$, $y = -32$, $z = -10$, $t = 4.42$, $k = 27$, P (FWE) $= 0.02$] than healthy matched controls (Fig. 2). Additionally, there was a trend for the right-sided MTL activation [$x = 32$, $y = -38$, $z = -10$, $t = 3.70$, $k = 13$, P (FWE) $= 0.12$]. No significant differences were observed in the opposite contrast (2 minus 0 back).

Discussion

To our knowledge, this is the first study that investigates MTL function and episodic memory performance among stroke patients. We found reduced MTL activation assessed by an *n*-back paradigm in stroke patients. In addition, stroke patients had a reduced episodic memory function compared to healthy matched controls.

A strong element in our study is the large sample size (28 stroke patients), in contrast with many other fMRI studies, which often investigated fewer than 20 patients (Meyer-Lindenberg *et al.*, 2001; Harvey *et al.*, 2005; Meisenzahl *et al.*, 2006) leading to the possibility of finding false negative results (type II error).

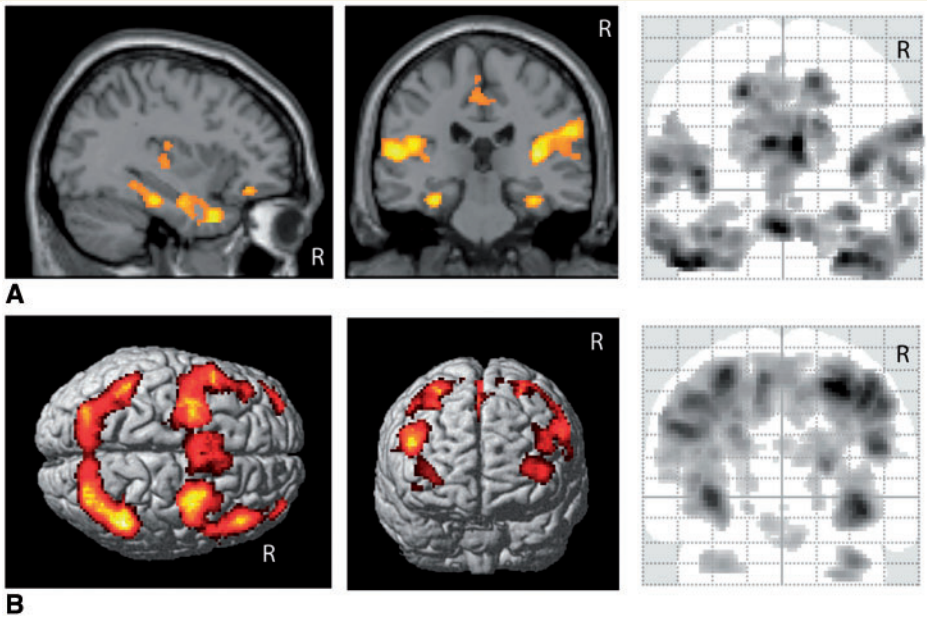

Figure 1 Whole brain activation pattern of 22 controls during (**A**) 0-back minus 2-back contrast and (**B**) 2-back minus 0-back contrast, thresholded at $P = 0.001$ uncorrected.

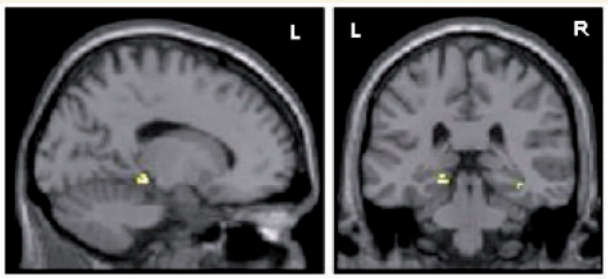

Figure 2 Difference in MTL activation between healthy controls ($n = 22$) and stroke patients ($n = 28$) during 0-back minus 2-back contrast. Healthy controls showed significantly more MTL activation than patients during the 0-back minus 2-back contrast, thresholded at $P = 0.001$ uncorrected.

Another strong element is our high response rate of 73%, which may imply a high-external validity. Furthermore, episodic memory was assessed blinded to MTL function. Another important issue is the generalized nature of our study, because we included all stroke patients regardless of the size and side of the infarction. This was done intentionally because a recent systematic review (Snaphaan and de Leeuw, 2007) found no evidence between lesion location and memory dysfunction. Therefore, our findings may be generalized towards any 'first-ever' stroke patient with an acute symptomatic supratentorial cerebral infarction.

However, there are also some methodological aspects that need to be considered. We used the activations in the MTLs in a working memory task to assess the 'functionality' of the MTLs in an episodic memory task. This is in line with previous research that used a similar approach (Johnson *et al*., 2001; Egan *et al*., 2003). In accordance with these studies we also found a positive correlation between MTL activation in the 0-back minus 2-back contrast and performances on the California Verbal Learning Task in controls ($\beta = 0.48$, $P = 0.02$), but not in patients. This finding suggests that reduced MTL functionality may be responsible for the impaired post-stroke episodic memory function. Furthermore, one could question the validity of fMRI in patients with a compromised cerebrovascular circulation. fMRI relies on the Blood Oxygen Level Dependent signal that is presumably dependent on intact cerebrovascular responses. However, the fact that we were able to detect fMRI responses as predicted from previous studies that used the *n*-back task (Callicott *et al*., 1999, 2000; Meyer-Lindenberg *et al*., 2001) makes this unlikely. In addition, recent methodological studies on the validity of functional MRI in stroke patients confirmed its usefulness (Kimberley *et al*., 2008).

Critics could argue that reduced MTL activation is simply a consequence of impaired performance on the *n*-back task by the stroke patients. However, despite the fact that patients performed worse on the delayed recall task, they did not on the *n*-back task; making this explanation rather unlikely. Another explanation for our finding of a reduced MTL activation among stroke patients could be differential selection of patients with already pre-existing cognitive decline. However, this seems unlikely as we only included patients that showed no signs of pre-stroke cognitive decline, as assessed with the IQCODE. Furthermore, memory function is known to be affected by many environmental factors and structural brain correlates including depressive symptoms, anxiety, total brain volume and hippocampal volume (Sullivan *et al*., 1996; Lupien *et al*., 1998; Kauhanen *et al*., 1999; Kizilbash *et al*., 2002). As patients were carefully matched with controls with respect to these factors, we consider it unlikely

that this differential MTL activation is explained by other group differences, except for the stroke.

Another explanation for a reduced MTL functionality could be a systemic reaction as a response to a cerebral event. Support from this notion comes from a study that found increased glucocorticoids levels in acute stroke patients compared with controls (Szczudlik *et al*., 2004). Subsequently, several studies have demonstrated that elevated glucocorticoids levels results in a reduction of hippocampal volume and deficits in hippocampus-dependent memory tasks compared with normal glucocorticoids controls (Lupien *et al*., 1998; de Quervain *et al*., 2003; Elgh *et al*., 2006). However, we consider this explanation unlikely as both episodic memory assessment and the fMRI experiments were performed ~2–3 months after the qualifying stroke. Longitudinal studies on the time-course of glucocorticoids levels after stroke have shown normalization within weeks after the stroke (O'Neill *et al*., 1991; Marklund *et al*., 2004; Cohan *et al*., 2005; Ibrahimagic *et al*., 2005).

Emerging evidence from functional neuroimaging, neurophysiology and computational modelling highlights the importance of interaction between the MTL, parietal cortex, thalamus and prefrontal cortex for a proper episodic memory function (Simons and Spiers, 2003). Any lesion or disconnection in this network [due to for example an infarction in white matter structures that connect the MTL with the other relevant structures or due to underlying psychiatric disease including schizophrenia (Callicott *et al*., 2000)] may result in an accompanying memory dysfunction, possibly due to a lesser functionality of the MTL or of any other element of the network. Support for this notion comes from a diffusion tensor imaging study among patients with traumatic brain injury (Kraus *et al*., 2007). In this study, Kraus and colleagues found that focal traumatic white matter abnormalities (not located in the MTL) were related to memory dysfunction. So, MTL functionality seems to depend on intact connections of the MTL with other brain regions and this functionality can be reduced due to disruptions of the connecting fibre tracts. Consequently, one could argue that stroke patients with an episodic memory function comparable with controls presumably would have a 'normal' MTL functionality as well. Unfortunately, our sample of stroke patients was too small to reliably compare 'normal' with 'impaired' episodic memory performers.

Clinically, our study could contribute to the early identification of stroke patients with reduced episodic memory function due to impaired MTL functionality. By and large, stroke patients are at increased risk for developing post-stroke dementia (Loewenstein *et al*., 2004) [which is three times higher than the risk of a recurrent stroke (Yokota *et al*., 2004)]. To date it is not possible to identify those at risk, but our study may provide diagnostic opportunities in this identification. Prospective studies are now needed to determine whether those with impaired MTL functionality are indeed at increased risk for post-stroke dementia. To unravel the underlying mechanisms of impaired MTL functionality some of these studies should investigate stroke patients with infarcts at similar locations with the aid of diffusion tensor imaging to study their effect on (loss of) connectivity within the episodic memory network.

References

Brierley B, Shaw P, David AS. The human amygdala: a systematic review and meta-analysis of volumetric magnetic resonance imaging. Brain Res Brain Res Rev 2002; 39: 84–105.

Brott T, Adams HP Jr, Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989; 20: 864–70.

Callicott JH, Bertolino A, Mattay VS, Langheim FJ, Duyn J, Coppola R, et al. Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. Cereb Cortex 2000; 10: 1078–92.

Callicott JH, Mattay VS, Bertolino A, Finn K, Coppola R, Frank JA, et al. Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. Cereb Cortex 1999; 9: 20–6.

Cohan P, Wang C, McArthur DL, Cook SW, Dusick JR, Armin B, et al. Acute secondary adrenal insufficiency after traumatic brain injury: a prospective study. Crit Care Med 2005; 33: 2358–66.

de Jonghe JF, Schmand B, Ooms ME, Ribbe MW. Abbreviated form of the informant questionnaire on cognitive decline in the elderly. Tijdschr Gerontol Geriatr 1997; 28: 224–9.

de Quervain DJ, Henke K, Aerni A, Treyer V, McGaugh JL, Berthold T, et al. Glucocorticoid-induced impairment of declarative memory retrieval is associated with reduced blood flow in the medial temporal lobe. Eur J Neurosci 2003; 17: 1296–302.

Delis DC, Kramer J, Kaplan E, Ober BA. California verbal learning test. Research edition edn., New York: The Psychological Corporation Harcourt Brace Jovanovich Inc; 1987.

Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 2003; 112: 257–69.

Elgh E, Lindqvist AA, Fagerlund M, Eriksson S, Olsson T, Nasman B, et al. Cognitive dysfunction, hippocampal atrophy and glucocorticoid feedback in Alzheimer's disease. Biol Psychiatry 2006; 59: 155–61.

Folstein M, Folstein S, McHugh PR. Clinical predictors of improvement after electroconvulsive therapy of patients with schizophrenia, neurotic reactions, and affective disorders. Biol Psychiatry 1973; 7: 147–52.

Friston KJ, Holmes AP, Worsley KJ, Poline JB, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapp 1995; 2: 189–210.

Geuze E, Vermetten E, Bremner JD. MR-based in vivo hippocampal volumetrics: review of methodologies currently employed. Mol Psychiatry 2005; 10: 147–59.

Harvey PO, Fossati P, Pochon JB, Levy R, Lebastard G, Lehericy S, et al. Cognitive control and brain resources in major depression: an fMRI study using the *n*-back task. Neuroimage 2005; 26: 860–9.

Hermann BP, Wyler AR, Richey ET, Rea JM. Memory function and verbal learning ability in patients with complex partial seizures of temporal lobe origin. Epilepsia 1987; 28: 547–54.

Hofgren C, Bjorkdahl A, Esbjornsson E, Sunnerhagen KS. Recovery after stroke: cognition, ADL function and return to work. Acta Neurol Scand 2007; 115: 73–80.

Ibrahimagic OC, Sinanovic O, Cickusic A, Smajlovic D. Ischemic stroke as reaction to an acute stressful event. Med Arh 2005; 59: 79–82.

Johnson SC, Saykin AJ, Flashman LA, McAllister TW, Sparling MB. Brain activation on fMRI and verbal memory ability: functional neuroanatomic correlates of CVLT performance. J Int Neuropsychol Soc 2001; 7: 55–62.

Kauhanen M, Korpelainen JT, Hiltunen P, Brusin E, Mononen H, Maatta R, et al. Poststroke depression correlates with cognitive impairment and neurological deficits. Stroke 1999; 30: 1875–80.

Kimberley TJ, Khandekar G, Borich M. fMRI reliability in subjects with stroke. Exp Brain Res 2008; 186: 183–90.

Kizilbash AH, Van der ploeg RD, Curtiss G. The effects of depression and anxiety on memory performance. Arch Clin Neuropsychol 2002; 17: 57–67.

Kraus MF, Susmaras T, Caughlin BP, Walker CJ, Sweeney JA, Little DM. White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. Brain 2007; 130: 2508–19.

Loewenstein DA, Acevedo A, Czaja SJ, Duara R. Cognitive rehabilitation of mildly impaired Alzheimer disease patients on cholinesterase inhibitors. Am J Geriatr Psychiatry 2004; 12: 395–402.

Lupien SJ, de Leon M, de Santi S, Convit A, Tarshish C, Nair NP, et al. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. Nat Neurosci 1998; 1: 69–73.

Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. MD State Med J 1965; 14: 61–5.

Marklund N, Peltonen M, Nilsson TK, Olsson T. Low and high circulating cortisol levels predict mortality and cognitive dysfunction early after stroke. J Intern Med 2004; 256: 15–21.

Meisenzahl EM, Scheuerecker J, Zipse M, Ufer S, Wiesmann M, Frodl T, et al. Effects of treatment with the atypical neuroleptic quetiapine on working memory function: a functional MRI follow-up investigation. Eur Arch Psychiatry Clin Neurosci 2006; 256: 522–31.

Meyer-Lindenberg A, Poline JB, Kohn PD, Holt JL, Egan MF, Weinberger DR, et al. Evidence for abnormal cortical functional connectivity during working memory in schizophrenia. Am J Psychiatry 2001; 158: 1809–17.

Mungas D, Ehlers C, Walton N, McCutchen CB. Verbal learning differences in epileptic patients with left and right temporal lobe foci. Epilepsia 1985; 26: 340–5.

O'Neill PA, Davies I, Fullerton KJ, Bennett D. Stress hormone and blood glucose response following acute stroke in the elderly. Stroke 1991; 22: 842–7.

Rasquin SM, Lodder J, Ponds RW, Winkens I, Jolles J, Verhey FR. Cognitive functioning after stroke: a one-year follow-up study. Dement Geriatr Cogn Disord 2004; 18: 138–44.

Simons JS, Spiers HJ. Prefrontal and medial temporal lobe interactions in long-term memory. Nat Rev Neurosci 2003; 4: 637–48.

Snaphaan L, de Leeuw FE. Poststroke memory function in nondemented patients: a systematic review on frequency and neuroimaging correlates. Stroke 2007; 38: 198–203.

Sullivan EV, Shear PK, Lim KO, Zipursky RB, Pfefferbaum A. Cognitive and motor impairments are related to gray matter volume deficits in schizophrenia. Biol Psychiatry 1996; 39: 234–40.

Suzuki WA. Integrating associative learning signals across the brain. Hippocampus 2007; 17: 842–50.

Szczudlik A, Dziedzic T, Bartus S, Slowik A, Kieltyka A. Serum interleukin-6 predicts cortisol release in acute stroke patients. J Endocrinol Invest 2004; 27: 37–41.

van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988; 19: 604–7.

Verhage F. Inteligence and age. Assen: Van Gorcum; 1964.

Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjogren M, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 2001; 32: 1318–22.

Weinberger DR, Mattay V, Callicott J, Kotrla K, Santha A, van Gelderen P, et al. fMRI applications in schizophrenia research. Neuroimage 1996; 4: S118–26.

Worsley KJ, Marrett S, Neelin P, Vandal AC, Friston KJ, Evans AC. A unified statistical approach for determining significant signals in images of cerebral activation. Hum Brain Mapp 1996; 4: 58–73.

Yokota C, Minematsu K, Hasegawa Y, Yamaguchi T. Long-term prognosis, by stroke subtypes, after a first-ever stroke: a hospital-based study over a 20-year period. Cerebrovasc Dis 2004; 18: 111–6.

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67: 361–70.