Frequency and clinical, neuropsychological and neuroimaging correlates of apathy following stroke – the Sydney Stroke Study

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ABSTRACT

Background. The frequency and clinical, neuropsychological and neuroimaging correlates of apathy in patients who have had a stroke are inadequately defined.

Method. A total of 167 consecutive patients admitted to the stroke units of two university hospitals after an ischaemic stroke and 109 controls received extensive medical, psychiatric and neuropsychological assessments; a subset received a magnetic resonance imaging (MRI) scan. The groups were matched for sex and age. Patients were assessed 3–6 months after their stroke. The sample for this study comprised 135 patients and 92 controls who completed the Apathy Evaluation Scale (AES).

Results. Apathy was present in 26.7% of stroke patients compared to 5.4% of controls. Apathetic stroke patients were older, more functionally dependent and had lower Mini-Mental State Examination (MMSE) scores than those without apathy. Apathy was not associated with risk factors for cerebrovascular disease or stroke severity. There was a weak but significant correlation between apathy and self-reported depression but not with clinician-rated depression. Neuropsychologically, after correction for age, premorbid intelligence (IQ) and depression, apathy was associated with reduced attention and speed of information processing. On neuroimaging there were trends for associations of apathy with the extent of hyperintensities in the right hemisphere and right fronto-subcortical circuit, but not with total stroke volume or number of strokes.

Conclusions. Apathy is common following a cerebrovascular event. Presence of apathy may be related to older age and right fronto-subcortical pathway pathology, rather than stroke severity. It is associated with functional impairment and cognitive deficits.

INTRODUCTION

Until recently, the concept of apathy has been poorly conceptualized and many terms have been used to describe it (Brown & Pluck, 2000). Marin (1991) defined the apathy syndrome as a ‘simultaneous decrease in the behavioural, cognitive and emotional concomitants of goal-directed behaviour’ due to loss of motivation.

Apathy is evidenced by symptoms such as poor effort, lost will to engage in new or social activities, decreased self-concern, low positive and negative responsivity and flat affect (Marin, 1996). Apathy has sometimes been regarded as a symptom of depression, even though their severities are usually only weakly correlated (Marin et al. 1994; Levy et al. 1998; Andersson et al. 1999). Reported rates of apathy after
cerebrovascular accidents (CVAs) vary between 23% and 57%, possibly due to differences in the severity and location of cortical damage, as well as the method of measurement (Andersson et al. 1999; Starkstein et al. 1993; Okada et al. 1997).

Reported correlates of apathy after stroke are advancing age, deficits in activities of daily living (Starkstein et al. 1993), lower global cognitive function (Starkstein et al. 1993; Yamagata et al. 2004) and poor verbal fluency (Okada et al. 1997; Yamagata et al. 2004). Neuroimaging findings in stroke patients have been inconsistent, with reports of left (Robinson & Starkstein, 1990), right (Gainotti, 1972; Robinson et al. 1984; Marin et al. 1993) and bilateral cerebral dysfunction (Okada et al. 1997). Structural correlates of apathy have included posterior limb of the internal capsule pathology (Helgason et al. 1988; Starkstein et al. 1993), thalamic infarction (Bogousslavsky et al. 1991; Ghika-Schmid & Bogousslavsky, 2000) and no significant associations (Marin, 1991; Starkstein et al. 1993).

In view of the lack of clear findings and relatively few reported investigations, we aimed to study the frequency and clinical, neuropsychological and neuroimaging correlates of apathy in a cohort of patients 3–6 months after their admission to hospital for stroke. We hypothesized that: (1) using a case-control study design, the frequency and level of apathy would be increased in stroke patients compared with normal elderly controls; and (2) apathy in stroke patients would be associated with older age, more severe stroke, increased functional dependence, lower Mini-Mental State Examination (MMSE) score and executive dysfunction.

METHOD

Subjects
Consecutive eligible patients hospitalized for ischaemic stroke and control subjects were asked to participate (see procedure, below). An ischaemic stroke was defined as ‘rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer, with no apparent cause other than of vascular origin’ in which a brain computerized tomography (CT) or magnetic resonance imaging (MRI) scan does not show intracranial haemorrhage (Kunitz et al. 1984). Exclusion criteria were: age >85 years; haemorrhagic stroke; transient ischaemic attack (TIA); impairment of consciousness persisting for more than 7 days at time of stroke; inability to give informed consent; insufficient fluency in English to complete testing procedures; past history of dementia or other neurological disease known to affect cognition or alcohol or drug abuse; a retrospective score on the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE; Jorm, 1994) of >3·31 (indicating possible dementia prior to the index stroke); a DSM-IV (APA, 1994) diagnosis of mental retardation; severe aphasia (<3 on the Aphasia Severity Rating Scale of the Boston Diagnostic Aphasia Examination; Goodglass & Kaplan, 1983); and lack of an appropriate informant. Controls were excluded if they had a history of stroke or any of the above exclusion criteria.

From consecutive admissions over a 38-month period between May 1997 and June 2000 to the in-patient stroke units at Prince of Wales and St George Hospitals in Sydney, Australia, 205 patients met inclusion and exclusion criteria and gave consent for entry into the study. By the time of detailed assessment at 3–6 months following the cerebrovascular event, 38 were lost to follow-up (28 due to withdrawal, 3 died, 4 relocated outside Sydney, 2 were not contactable and 1 was excluded for baseline dementia/aphasia missed earlier). The remaining 167 eligible patients were scheduled for a medical/psychiatric and neuropsychological assessments at 3–6 months; 135 completed the Apathy Evaluation Scale (AES) and comprised the sample of interest for this paper.

A total of 130 controls recruited by advertisement and via local community groups met eligibility criteria of whom 21 declined to participate prior to baseline assessment; a total of 109 were assessed and 92 completed the AES. The controls and stroke patient groups were matched for sex and age. Stroke subjects were assessed comprehensively 3–6 months after their stroke. The study had institutional ethics committee approval and subjects provided written informed consent after receiving a complete description of the study.
Clinical measures
Stroke diagnoses were made according to ICD-10 criteria (WHO, 1992) and confirmed by consensus at team clinical meetings. Severity was established using the European Stroke Scale (ESS; Hantson et al., 1994). Functional ability was measured using the Activities of Daily Living (ADL; Katz & Akpom, 1976) and Instrumental Activities of Daily Living scales (IADL; Lawton & Brody, 1969). Cerebrovascular risk factors and alcohol use were recorded.

Psychiatric measures
Measures of psychiatric disturbance were made using the Structured Clinical Interview for DSM-IV (SCID-I; First et al., 1997), the 17-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960), 15-item Geriatric Depression Scale (GDS; Sheikh & Yesavage, 1986), informant-rated version of the AES (Marin et al., 1991) and details of past psychiatric history. The informant version of the AES was chosen because it performs better than the clinician-rated and self-rated forms of the scale with respect to internal consistency ($\alpha = 0.94$) and test–retest reliability ($r = 0.94$) (Marin et al., 1991). Diagnosis of dementia was made according to DSM-IV criteria and confirmed by consensus at team clinical meetings.

Patients were subdivided into those with apathy scores on the AES of <37 and those scoring $\geq 37$, representing $>2$ s.d. from the mean score of the control group (Kant et al., 1998; Andersson et al., 1999). This cut-off score is consistent with another sample of well elderly; mean age of 68.1 years (Marin et al., 1994).

Neuropsychological measures
Global cognitive function was assessed with the MMSE (Folstein et al., 1975) and premorbid intelligence assessed with the National Adult Reading Test – Revised (NART-R; Nelson, 1983). The IQCODE was rated retrospectively in the 5 years prior to the stroke as an indicator of premorbid cognitive decline. Handedness was determined using an abbreviated version of Annett’s test (Briggs & Nebes, 1975).

Neuropsychological tests were grouped into the following domains: (i) Attention and Concentration – Wechsler Adult Intelligence Scale – Revised (WAIS-R; Wechsler, 1981) Digit Span – forwards and Wechsler Memory Scale – Revised (WMS-R; Wechsler & Stone, 1987) Mental control subtest; (ii) Immediate Recall – WMS-R Logical Memory I and WMS-R Visual Reproduction I; (iii) Delayed Recall – WMS-R Logical Memory II and WMS-R Visual Reproduction II; (iv) Working Memory – WAIS-R Arithmetic subtest and WAIS-R Digit Span – backwards; (v) Executive Function – Colour Form Sorting Test (Goldstein & Scheerer, 1941; Weigl, 1941), Verbal Fluency phonemic (FAS; Benton & Hamsher, 1976) and semantic (animals; Morris et al., 1989), and Trail Making Test Part B (Reitan & Wolfson, 1985); (vi) Reasoning – WAIS-R Similarities and Picture Completion subtests; (vii) Language – 15-item Boston Naming Test (BNT; Kaplan et al., 1978); (viii) Visuoconstruction/Praxis – WAIS-R Block Design subtest – Copying and Western Aphasia Battery ideomotor apraxia subtest (Kertesz, 1982) and (ix) Speed of Information Processing – Trail Making Test Part A and Symbol Digit Modalities Test – oral (Smith, 1991). Trained psychologists performed all tests. Neuropsychological assessments of subjects judged to be significantly depressed at clinical interview were deferred until patients improved. This was defined as either a GDS score of $<5$, a reduction in self- or informant-reported symptoms and/or a further psychiatric assessment of improvement. Subjects were tested in their own homes and given breaks during testing to minimize fatigue. Those with right- or left-sided paresis were not tested on motor tasks requiring the use of the affected side.

Neuroimaging
All patients received either a CT or MRI scan at baseline, and a subset had an MRI scan 3–6 months later, at approximately the same time as their neuropsychological assessment. Only the 3–6 months MRI data are presented here. Controls were asked to have an MRI scan at baseline assessment. MRI was performed on a 1.5 T Signa GE scanner (GE Systems, Milwaukee, WI, USA) using the following protocol: a scout mid-sagittal cut (2D, repetition time TR 300 ms, echo time TE 14 ms; 5-mm thick, number of excitations 1-5); 1.5-mm-thick T1-weighted contiguous coronal
sections through the whole brain using a FSPGR sequence (TR 14.3 ms, TE 5.4 ms); and 4-mm-thick (0 skip) T2-weighted fluid attenuation inversion recovery (FLAIR) coronal slices through the whole brain (TR 8900, TE 145, TI 2200, FOV 25, 256 × 192). Trained staff scored these with good inter-rater (kappa scores from 0.7 to 0.9 on various measures) and intra-rater (kappa = 0.8 to 0.9) reliability. ANALYZE (Mayo Foundation, Rochester, MI, USA) software was used for all ratings. Periventricular (PVH) and deep white-matter hyperintensities (DWMH) were rated on a 0–3 scale, with higher score representing more pathology (Fazekas et al. 1987). For PVH, ratings were performed for the lining of the lateral ventricles (rims) and the frontal and occipital horns (caps), the sum of which on either side gave the total PVH score (maximum score 18). For DWMH rating, the frontal, temporo-parietal and occipital white matter, and the internal capsules were rated separately, and the scores for both sides added to give a total DWMH score (maximum score = 24). In rating DWMHs, peri-infarct hyperintensities were disregarded. The DWMHs are, therefore, non-infarct lesions on FLAIR T2-weighted imaging that are not related to an actual infarct as seen on either T1- or T2-weighted imaging. Cortical atrophy was rated on a 0–2 scale in the frontal, temporal and mid-parietal regions, the sum of which gave the cortical atrophy score (higher scores = more atrophy, maximum score = 6). As a measure of subcortical atrophy, two ventricle–brain ratios (VBRs), anterior and mid-section, were obtained (Victoroff et al. 1994).

Stroke characteristics determined from 3-month MRI scans were number of infarcts (large infarcts and lacunes), number of right- or left-sided recent infarcts (this was a clinical determination based on neuroimaging, history and clinical findings), total volume of infarction, and number with no infarcts on MRI scan. Where necessary, determination of the site of the new lesion for stroke patients was made at a consensus conference using clinical and baseline neuroimaging data. Atrophy measures used were cortical (sum of three cortical regions) and frontal, as well as the anterior and mid-VBR. White-matter disease was calculated for the left hemisphere, right hemisphere, anterior brain (frontal region + anterior horn), posterior brain (occipital region + posterior cap), whole brain, periventricular region, deep white matter and internal capsule. Hyperintensity scores were obtained separately for the right and left fronto-subcortical circuits, which comprised the ipsilateral frontal white matter, anterior capsule, basal ganglia and thalamus.

Statistical analyses

The Statistical Package for the Social Sciences (SPSS) version 10 for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Independent-sample t tests were employed for between-group comparisons on continuous variables. Univariate analyses of the association between patient and control demographics were performed using χ² analysis. For 2 × 2 tables, Yates’ continuity correction is reported. Fisher’s exact test was used in the analysis of 2 × 2 tables with expected frequencies lower than five in two or more cells. Odds ratios were calculated for the relative risk of psychiatric disorders for each group. For all analyses, probability levels reported were two-tailed, and the level of significance was set at 0.05.

z scores for neuropsychological domains were derived from raw scores, normed by control data. For each domain, individual z scores were added up and divided by the number of tests that comprised the domain.

Groups were compared on demographic variables, presence of cerebrovascular risk factors and neuroimaging data. Neuropsychological tests were grouped into their cognitive domains and partial correlations were calculated, correcting for the effects of age, premorbid IQ and depression severity. In order to remove the possible impact of depression on apathy ratings, relevant comparisons of apathetic and non-apathetic subjects were controlled for severity of depression using a 14-item HRSD score and 12-item GDS. The HRSD-14 was calculated as the total 17-item HRSD score minus three likely ‘apathy items’ (i.e. Item 7 ‘Work and activities’, Item 8 ‘Psychomotor retardation’, and Item 13 ‘Somatic symptoms general’). The GDS-12 was calculated as the total 15-item GDS minus three possible apathy items (i.e. Item 2 ‘Have you dropped many of your activities and interests?’, Item 9 ‘Do you prefer to rather stay at home than going out and doing new things?’, and Item 13 ‘No energy’).
RESULTS

The sample

Of the 205 stroke patients recruited at baseline, there were no significant differences between the 167 patients who completed the 3–6 months follow-up assessment and the 38 who did not with respect to age (t = −1.10, p = 0.27), education (t = −0.91, p = 0.36) or sex (χ² = 3.19, p = 0.07).

Of the 167 patients followed up, there were no significant differences between the 135 stroke patients who completed the AES and the 32 who did not with respect to age (t = 0.52, p = 0.61), sex (χ² = 3.49, p = 0.06), MMSE (t = −1.33, p = 0.21), ADL (t = 0.88, p = 0.39) and IADL scores (t = 0.33, p = 0.74). However, the non-AES completers were less educated (t = −2.10, p = 0.04).

Demographic characteristics of the stroke and control samples did not differ significantly except that stroke patients were less educated and had lower premorbid IQ. As anticipated, stroke patients were performing their ADLs and IADLs more poorly and had lower MMSE scores. Their levels of depression were higher but few stroke patients met criteria for a diagnosis of depression (Table 1).

Rate of apathy in stroke patients and controls and its relation to depression

Rates of apathy were significantly higher among stroke patients than controls (Table 1). Of the

Table 1. Demographic and clinical comparisons of controls versus stroke patients and apathetic versus non-apathetic stroke patients

<table>
<thead>
<tr>
<th></th>
<th>Total sample</th>
<th>Stroke sample</th>
<th>Apathetic (n = 36)</th>
<th>Non-apathetic (n = 99)</th>
<th>t value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controls</strong></td>
<td>(n = 92)</td>
<td>(n = 135)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td>71.4 (6.5)</td>
<td>72.2 (8.8)</td>
<td>−8.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex (male)</strong></td>
<td>44 (47.8%)</td>
<td>82 (60.7%)</td>
<td>χ² = 3.19</td>
<td>14 (61.1%)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Education (yr)</strong></td>
<td>11.8 (3.4)</td>
<td>10.2 (2.8)</td>
<td>3.66b</td>
<td>9.8 (3.0)</td>
<td>1.27</td>
</tr>
<tr>
<td><strong>NART-R IQ</strong></td>
<td>113.9 (7.9)</td>
<td>104.3 (10.3)</td>
<td>7.68b</td>
<td>101.8 (9.4)</td>
<td>1.52</td>
</tr>
<tr>
<td><strong>IQCODE</strong></td>
<td>3.09 (0.2)</td>
<td>3.02 (0.6)</td>
<td>1.01</td>
<td>3.24 (0.5)</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>ESS</strong></td>
<td>—</td>
<td>93.5 (10.0)</td>
<td></td>
<td>91.8 (10.4)</td>
<td>1.05</td>
</tr>
<tr>
<td><strong>ADL</strong></td>
<td>5.97 (0.23)</td>
<td>5.07 (1.51)</td>
<td>6.75b</td>
<td>4.31 (1.78)</td>
<td>3.14a</td>
</tr>
<tr>
<td><strong>IADL</strong></td>
<td>7.52 (1.14)</td>
<td>6.60 (2.07)</td>
<td>4.30b</td>
<td>5.31 (2.44)</td>
<td>3.99b</td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td>28.8 (1.3)</td>
<td>27.9 (2.4)</td>
<td>3.40b</td>
<td>26.8 (3.3)</td>
<td>2.56b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Stroke sample</th>
<th>Apathetic (n = 36)</th>
<th>Non-apathetic (n = 99)</th>
<th>t value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td>71.1 (9.2)</td>
<td>75.2 (7.0)</td>
<td>−2.72b</td>
<td></td>
</tr>
<tr>
<td><strong>Sex (male)</strong></td>
<td>16.7 (5.0)</td>
<td>14 (61.1%)</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td><strong>Education (yr)</strong></td>
<td>10.2 (2.8)</td>
<td>9.8 (3.0)</td>
<td>1.27</td>
<td></td>
</tr>
<tr>
<td><strong>NART-R IQ</strong></td>
<td>104.3 (10.3)</td>
<td>101.8 (9.4)</td>
<td>1.52</td>
<td></td>
</tr>
<tr>
<td><strong>IQCODE</strong></td>
<td>3.02 (0.6)</td>
<td>3.24 (0.5)</td>
<td>0.79</td>
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</tr>
<tr>
<td><strong>ESS</strong></td>
<td>93.5 (10.0)</td>
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<td>4.31 (1.78)</td>
<td>3.14a</td>
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<tr>
<td><strong>IADL</strong></td>
<td>6.60 (2.07)</td>
<td>5.31 (2.44)</td>
<td>3.99b</td>
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<td><strong>MMSE</strong></td>
<td>27.9 (2.4)</td>
<td>26.8 (3.3)</td>
<td>2.56b</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Psychiatric Rating Scales</strong></th>
<th>Stroke sample</th>
<th>Apathetic (n = 36)</th>
<th>Non-apathetic (n = 99)</th>
<th>t value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AES (≥37)</td>
<td>32.2 (10.3)</td>
<td>24.1 (6.2)</td>
<td>−7.29b</td>
<td>-4.12b</td>
</tr>
<tr>
<td>AES (% &gt;37)</td>
<td>26.7</td>
<td>16.1 (1.9)</td>
<td>2.7 (3.6)</td>
<td>3.6 (4.9)</td>
</tr>
<tr>
<td>17-item HRSD</td>
<td>8.2 (3.6)</td>
<td>5.2</td>
<td>3.66b</td>
<td>8.0 (2.0)</td>
</tr>
<tr>
<td>17-item HRSD (% &gt;10)</td>
<td>2.9 (2.8)</td>
<td>1.3 (1.6)</td>
<td>5.37b</td>
<td>4.0 (3.4)</td>
</tr>
<tr>
<td>15-item GDS</td>
<td>16.0</td>
<td>1.3 (1.6)</td>
<td>8.17b</td>
<td>21.9 (3.4)</td>
</tr>
<tr>
<td>DSM-IV Major Depression (%)</td>
<td>4.4</td>
<td>1.2</td>
<td>0.37</td>
<td>8.6 (3.4)</td>
</tr>
<tr>
<td>DSM-IV Minor Depression (%)</td>
<td>4.4</td>
<td>1.2</td>
<td>0.37</td>
<td>8.2 (2.5)</td>
</tr>
<tr>
<td>DSM-IV Dementia (%)</td>
<td>2.4</td>
<td>92.2</td>
<td>0.37</td>
<td>52.9 (14.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>62.9</td>
<td>37.1</td>
<td>2.9a</td>
<td>65.6 (6.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16.8</td>
<td>5.7</td>
<td>3.4a</td>
<td>21.2 (15.3)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>41.1</td>
<td>24.7</td>
<td>2.1a</td>
<td>46.0 (41.3)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>32.8</td>
<td>16.9</td>
<td>2.44</td>
<td>34.4 (32.3)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>13.2</td>
<td>2.4</td>
<td>0.34</td>
<td>15.6 (12.4)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>25.6</td>
<td>2.3</td>
<td>0.34</td>
<td>31.3 (23.7)</td>
</tr>
<tr>
<td>Smoking</td>
<td>66.4</td>
<td>40.9</td>
<td>2.9a</td>
<td>65.6 (66.7)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>7.6</td>
<td>5.9</td>
<td>0.37</td>
<td>9.4 (7.1)</td>
</tr>
</tbody>
</table>

NART-R IQ, National Adult Reading Test Intelligence Quotient; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; ESS, European Stroke Scale; ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; MMSE, Mini-Mental State Examination; AES, Apathy Evaluation Scale; HRSD, Hamilton Rating Scale for Depression; GDS, Geriatric Depression Scale; N.A., not applicable as dementia was an exclusion criteria for controls when assessed at baseline.

a Significant at 0.05; b significant at 0.01; c significant at 0.001.
2.22, 95% CI 0.71–6.95) between apathy and non-apathetic stroke patients also did not differ on the modified HRSD-14 score (r = 0.18). Apathy even when the three apathy-related items were removed (t = −1.60, p = 0.12). Apathetic and non-apathetic stroke patients also did not differ on the modified HRSD-14 score (t = −0.52, p = 0.60).

Comparison of patients with and without apathy

Clinical and psychiatric measures

Compared to stroke patients without apathy, those with apathy were significantly older, had lower MMSE scores, and were less independent in ADL/IADLs (Table 1). There were no significant differences in gender, education, presence of cerebrovascular risk factors, or ESS-measured severity of stroke. Stroke patients with apathy were also more depressed than stroke patients without apathy according to the GDS but not the HRSD, although the level of symptoms was below usually accepted clinical thresholds. GDS scores remained higher, but not significantly so, in stroke patients with apathy even when the three apathy-related items were removed (t = −1.60, p = 0.12). Apathetic and non-apathetic stroke patients also did not differ on the modified HRSD-14 score (t = −0.52, p = 0.60).

Neuropsychological measures

The 7 out of 135 stroke patients rated on the AES who did not receive a neuropsychological assessment did not differ from the other 128 as regards age (t = −1.30, p = 0.20), sex (χ² = 0.36, p = 0.43), level of education (t = 1.04, p = 0.30), severity of stroke (t = −1.80, p = 0.08), ADLs (t = −0.13, p = 0.89) or IADLs (t = −0.78, p = 0.44). Only two of the 92 controls who completed the AES did not have a neuropsychological assessment; statistical comparisons were not calculated.

z scores calculated for neuropsychological domains are displayed in Table 2. Stroke patients performed more poorly than control subjects in all domains. Among the stroke patients, after a Bonferroni correction was applied, apathetic patients performed significantly worse in the areas of attention and concentration, working memory and reasoning.

Cognitive correlates of apathy in stroke patients were also examined using partial correlations. After correcting for age and pre-morbid IQ, apathy was significantly correlated with reductions in attention and concentration (r = −0.25, p = 0.007) and working memory (r = −0.23, p = 0.01) as well as slower speed of information processing (r = 0.30, p = 0.002). When an additional correction was made for depression severity (using the 14-item HRSD score), only the domains of attention and concentration (r = −0.29, p = 0.02) and speed of...
information processing ($r = 0.29$, $p = 0.02$) remained significant.

**Neuroimaging measures**

There were no differences between the 77 imaged and 58 non-imaged stroke patients who completed the AES with respect to age ($t = -0.39$, $p = 0.70$), sex ($\chi^2 = 0.38$, $p = 0.54$), level of education ($t = 0.14$, $p = 0.98$), MMSE ($t = -0.22$, $p = 0.83$), ADLs ($t = -1.35$, $p = 0.18$) or severity of stroke ($t = -1.73$, $p = 0.09$). Imaged stroke patients performed better on the IADLs (7.13 vs. 5.88, $t = -3.36$, $p = 0.001$). There were no differences between the 69 imaged and the 23 non-imaged controls who completed the AES with respect to age ($t = 1.26$, $p = 0.21$), sex ($\chi^2 = 1.45$, $p = 0.23$), level of education ($t = -0.28$, $p = 0.78$), MMSE ($t = -0.12$, $p = 0.91$), ADLs ($t = -2.6$, $p = 0.08$) or IADLs ($t = 0.84$, $p = 0.40$).

In the imaged stroke patients, there were no significant associations between apathy scores and total stroke volume, number of prior strokes or measures of atrophy. The only significant associations were between apathy and both right-sided and right fronto-subcortical circuit hyperintensity scores. These remained significant when controlled for age ($F = 6.14$, $p = 0.016$ and $F = 5.79$, $p = 0.019$), but not when a Bonferroni correction was applied to account for multiple $t$ tests (Table 3). The frequencies of large infarct ($\chi^2 = 0.58$, $p = 0.445$), lacunes ($\chi^2 = 0.37$, $p = 0.543$) or no infarct ($\chi^2 = 1.82$, $p = 0.177$) were also compared between groups with no significant differences. In addition, there were no differences between groups for VBR anterior ($t = 0.926$, $p = 0.357$) and VBR mid ($t = -0.305$, $p = 0.761$) as well as whole brain ($t = -1.81$, $p = 0.086$), anterior ($t = -1.19$, $p = 0.240$) and posterior ($t = -1.19$, $p = 0.239$) white matter hyperintensities.

**DISCUSSION**

Apathy was almost five times more common in stroke patients when examined 3–6 months after the index stroke than in controls, as defined by an AES score of $\geq 37$ (26.7% vs. 5.4% of controls). Our results are similar to the rate of 22% reported by Starkstein et al. (1993) in a stroke sample.

We confirmed that apathy was associated with older age, increased functional dependence and decreased global cognition (i.e. lower MMSE) (Starkstein et al. 1993). We did not find that apathy was correlated with stroke severity as measured by the ESS, suggesting this was not a direct effect of the physical dysfunction...
produced by the stroke. Apathetic subjects however had lower performances on ADL, IADL and cognitive tasks, raising the possibility that these may be consequences of apathy. Apathy was not found to be merely a proxy for dementia in this sample since 47.1% of the apathetic stroke sample did not meet criteria for diagnosis. Longitudinal data could show whether apathy may be an early prognostic marker for dementia, as suggested elsewhere (Bartolini et al. 2005).

Apathetic and non-apathetic stroke patients differed in the domains of attention and concentration, working memory, reasoning and speed of information processing. The association with working memory may be due to depression (Nebes et al. 2000), as the correlation became non-significant after a correction for HDRS-14 score. The reductions in concentration, reasoning skills and processing speed and the neuroimaging results support a pattern of frontal-subcortical dysfunction (Rao et al. 1997).

We had hypothesized that apathy would be associated with greater stroke volume. There was no association with either stroke volume or number of prior strokes. It is unlikely that the appearance of apathy is merely an index of the extent of damage to the brain, but is more likely determined by the lesion site and the specific neuronal circuits affected. Nor did we find evidence that apathy might be associated with events more distal to the stroke, e.g. risk factors for cerebrovascular disease. The main neuroimaging finding was significantly greater white-matter disease in apathetic patients in the right hemisphere, involving the pathway of right fronto-subcortical circuits, which encompassed the right frontal region, anterior capsule, basal ganglia and thalamus. This is consistent with suggestions that post-stroke apathy follows right-sided lesions, and may be due to dysfunction of the cortico-limbic reticular system, anterior cingulate and frontal areas, including dysfunction in the connections of these regions with the basal ganglia and thalamus (Cummings, 1993; Okada et al. 1997). The association of apathy with right hemispheric and subcortical lesions is supported by another study of traumatic brain injury and stroke (Andersson et al. 1999). These associations though, between right-sided hyperintensities and apathy, were not robust. No correction was made for multiple comparisons and correlations between AES score and right-sided or right fronto-subcortical circuit hyperintensity ratings were non-significant ($r=0.15$, $p=0.19$ and $r=0.14$, $p=0.20$ respectively), perhaps because of the small range in the hyperintensity scores (i.e. 0–3). However, comparisons of stroke subjects in the highest and lowest tertiles on AES score confirmed a difference in their right-sided hyperintensity scores ($t=-2.31, p=0.026$) but only a trend for right fronto-subcortical circuit hyperintensity scores ($t=-1.56, p=0.13$).

Our study supports the independence of apathy and depression as distinct but partially overlapping constructs (Marin et al. 1993; Starkstein et al. 1993; Andersson et al. 1999; Kuzis et al. 1999; Erhan et al. 2000). The correlation between the apathy and depression ratings was low. We judged that about one-quarter of the apathy group also had depression, which was less than the approximately 1-in-2 reported by Starkstein et al. (1993). This distinction between apathy and depression is consistent with the putative functional neuroanatomy of the two syndromes, with post-stroke depression linked to left anterior lesions (Robinson et al. 1984) and apathy to right hemispheric subcortical pathology (Andersson et al. 1999). Since stroke patients often have multiple brain lesions, the two can be concurrent.

The importance of recognizing apathy and distinguishing it from depression has ramifications for patients, especially as regards management (Marin, 1996), as well as their caregivers. Apathy increases the burden on caregivers who may misattribute the pathological loss of drive to laziness or defiance (Landes et al. 2001). Apathy is closely associated with longer hospital stay following stroke and these patients are less likely to seek out rehabilitation services (Galynker et al. 1997; Zawacki et al. 2002). As such, apathy may be related to less successful recovery. There are also different treatment regimens recommended for post-stroke depression and apathy, with the latter possibly benefiting from the use of dopaminergic or anticholinesterase medication (Galynker et al. 1997; Levy et al. 1998; Boyle & Malloy, 2004).

While the strengths of the study included a large sample and a broad neuropsychological battery, several methodological issues bear
comment. We included first and repeat stroke patients and there were no ratings of apathy prior to the index admission. Also, we note that our estimate of frequency is likely to be conservative, as the most apathetic patients may have preferentially not agreed to enrol in the study at baseline or to complete sections of the assessment protocol. Comparisons of study completers and drop-outs failed to find any significant differences on key variables. We acknowledge that apathy ratings were made by informants rather than patients themselves, however, this did not necessarily limit the accuracy as patients with apathy typically have poor insight into their own condition as well as lack of self-concern (Marin, 1990). It is also possible that the rate of apathy in the control population is an underestimate, since apathetic individuals are unlikely to participate in a fairly demanding study of this kind. A population-based study with a representative sample can resolve this issue.

We conclude that apathy is a common psychiatric condition after stroke, is distinct from but has some overlap with depression, is associated with functional impairment and cognitive deficits, in particular concentration and information processing speed, and may be secondary to pathology affecting right fronto-basal ganglia pathways. Apathy is more likely in older patients with poorer global cognitive function; effective treatment strategies for apathy are needed for this group of patients.

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DECLARATION OF INTEREST

None.


