Clinical deficits correlate with regional cerebral atrophy in progressive supranuclear palsy

N. J. Cordato,1 A. J. Duggins,2 G. M. Halliday,3 J. G. L. Morris2 and C. Pantelis4

1Department of Geriatric Medicine, Westmead Hospital and the University of Sydney, 2Department of Neurology, Westmead Hospital, Westmead, NSW, 3Prince of Wales Medical Research Institute and the University of New South Wales, Sydney, NSW and 4Melbourne Neuropsychiatry Centre, The University of Melbourne, Royal Melbourne and Sunshine Hospitals, Victoria Australia

Correspondence to: Dr N. J. Cordato, Department of Geriatric Medicine, Westmead Hospital, Westmead, NSW 2145, Australia
E-mail: Nicholas_Cordato@wsahs.nsw.gov.au

Summary
Most cerebral imaging studies of patients with progressive supranuclear palsy (PSP) have noted subtle atrophy, although the full extent of atrophy and any correlates to clinical features have not been determined. We used voxel-based morphometry analysis of grey matter, white matter and CSF on MRI brain scans to map the statistical probability of regional tissue atrophy in 21 patients with PSP, 17 patients with Parkinson’s disease and 23 controls. PSP and Parkinson’s disease cohorts were selected to approximate the mid-stages of their respective disease courses. Where regions of significant tissue atrophy were identified in a disease group relative to controls, the probability of tissue loss within those regions was correlated with global indices of motor disability, and behavioural and cognitive disturbance for that disease group. Minimal regional atrophy was observed in Parkinson’s disease. PSP could be distinguished from both controls and Parkinson’s disease by symmetrical tissue loss in the frontal cortex (maximal in the orbitofrontal and medial frontal cortices), subcortical nuclei (midbrain, caudate and thalamic) as well as periventricular white matter. For PSP, motor deficits correlated with atrophy of the caudate and motor cingulate, while behavioural changes related to atrophy in the orbitofrontal cortex and midbrain. These data suggest that intrinsic neurodegeneration of specific subcortical nuclei and frontal cortical subregions together contribute to motor and behavioural disturbances in PSP and differentiate this disorder from Parkinson’s disease within 2–4 years of symptom onset.

Keywords: Parkinson’s disease; progressive supranuclear palsy; regional brain atrophy; voxel-based morphometry

Abbreviations: BA = Brodmann area; FBI = Frontal Behavioural Inventory; H&Y = Hoehn and Yahr; MMSE = Mini-Mental State Examination; MNI = Montreal Neurological Institute; PSP = progressive supranuclear palsy; UPDRS = Unified Parkinson’s Disease Rating Scale; VBM = voxel-based morphometry


Introduction
Progressive supranuclear palsy (PSP), the second most common neurodegenerative movement disorder after idiopathic Parkinson’s disease, is characterized by early postural instability and supranuclear gaze palsy (Litvan, 1999; Nath et al., 2001). By mid-stage disease, the majority of PSP cases exhibit prominent frontal type behavioural disturbances (Litvan et al., 1996b; Cordato et al., 2002) and impaired executive function (Litvan et al., 1996b; Litvan, 1999). It has been thought that these latter clinical deficits result from neurodegeneration in subcortical brain structures disrupting the function of cortical–subcortical brain circuits (Cummings, 1993; Litvan et al., 1996b), even though significant frontal cortical atrophy in PSP has increasingly been recognized (Cordato et al., 2000, 2002; Brenneis et al., 2004; Groschel et al., 2004). In contrast, lobar atrophy is not a feature of Parkinson’s disease (Cordato et al., 2000, 2002).

Three previous studies have examined correlations between clinical deficits and regional brain atrophy in PSP (Cordato et al., 2000, 2002; Groschel et al., 2004). Using manual region of interest techniques for the entire frontal
lobe, we found that frontal grey atrophy correlates with increasing severity of behavioural and cognitive disturbances in mid- and end-stage PSP cases (Cordato et al., 2000, 2002). Behavioural deficits have also been correlated with variations in total frontal white matter volumes in PSP (Groschel et al., 2004). However, the topography of cortical atrophy within the frontal lobe grey and white matter that underlies these clinical deficits remains unclear. It is also possible that clinically relevant focal atrophy exists in cortical lobes in which overall tissue volume is preserved in either PSP or Parkinson’s disease.

These issues can now be explored further using voxel-based morphometry (VBM), an automated whole brain morphometric technique, which maps the statistical probability of regional tissue atrophy on a voxel by voxel basis. In the present study, VBM was used to characterize the distribution of cerebral atrophy in mid-stage PSP relative to Parkinson’s disease and matched controls, as well as to identify any clinical correlates.

Subjects and methods
Thirty-eight patients satisfying current clinical criteria for PSP (n = 21; Litvan et al., 1996a) or idiopathic Parkinson’s disease (n = 17; Gelb et al., 1999; Hughes et al., 1992) were examined for this study. All patients were recruited from the Movement Disorders Clinic of Westmead Hospital, a large University of Sydney teaching hospital, and by neurologists from the Sydney Movement Disorder Society. Five of the 21 PSP patients have since died. Post-mortem histopathology has confirmed definite PSP (Litvan et al., 1996a) in all five. For comparison, 23 normal controls without neurological, psychiatric or neuroradiological abnormalities were recruited from hospital and community volunteers, as well as spouses, caregivers and friends of the patients. The groups were matched for mean age, sex, handedness, mean peak adult height and, for the PSP and Parkinson’s disease groups, mid-stage disease (Cordato et al., 2002). Written informed consent was obtained for each subject according to the Declaration of Helsinki and the project was approved by the Human Research Committee of the Western Sydney Area Health Service.

The 38 patients and 23 matched controls underwent volumetric MRI brain scanning and standardized clinical assessment within 2 weeks of MRI acquisition. All MRI scanning was performed at Westmead Hospital, Sydney on the same Siemens Magnetom Vision 1.5 T scanner (Siemens AG, Erlangen, Germany). Scanning parameters and clinical procedures have been described in detail previously (Cordato et al., 2002). Briefly, three-dimensional magnetization-prepared rapid gradient echo (MPRAGE) sequences [repetition time (TR) 9.7 ms, echo time (TE) 4 ms, number of excitations (NEX) 1, flip angle 12°, 246 × 1.02 mm thick contiguous coronal slices] were used for the VBM analyses. Correlations between clinical scores and volumes of selected brain structures defined manually from these scans have been published previously (Cordato et al., 2002). Standardized clinical indices used in correlations were disease severity as measured by the Hoehn and Yahr scale (H&Y; Hoehn and Yahr, 1967) and the Unified Parkinson’s Disease Rating Scale (UPDRS; Fahn et al., 1987), as well as cognitive and behavioural disturbances estimated using the Mini-Mental State Examination (MMSE) and the 24-item Frontal Behavioural Inventory (FBI; Kertesz et al., 1997), respectively. For Parkinson’s disease cases with motor fluctuations (n = 12), disease severity indices are reported in the off state (i.e. when levodopa effects wore off), whilst cognitive/behavioural indices were acquired in the on phase (i.e. when levodopa was having a beneficial clinical effect). Demographic data for the study groups are shown in Table 1.

**Table 1 Demographics and disease severity indices**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>PSP</th>
<th>Parkinson’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M : F)</td>
<td>14 : 9</td>
<td>14 : 7</td>
<td>13 : 4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71.5 ± 7.2</td>
<td>70.3 ± 6.4</td>
<td>67.7 ± 6.7</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>N/A</td>
<td>47.7 ± 34.0*</td>
<td>94.3 ± 35.5</td>
</tr>
<tr>
<td>UPDRS-total score</td>
<td>0.6 ± 1.7</td>
<td>45.1 ± 20.2*</td>
<td>32.3 ± 12.5</td>
</tr>
<tr>
<td>UPDRS-motor score</td>
<td>0.3 ± 0.5</td>
<td>23.1 ± 10.1</td>
<td>18.9 ± 7.4</td>
</tr>
<tr>
<td>H&amp;Y stage</td>
<td>0 ± 0</td>
<td>3.8 ± 1.1*</td>
<td>2.6 ± 0.7</td>
</tr>
<tr>
<td>FBI</td>
<td>0.2 ± 0.8</td>
<td>21.3 ± 12.0*</td>
<td>4.9 ± 4.5</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.4 ± 0.9</td>
<td>25.4 ± 3.2</td>
<td>28.6 ± 1.2</td>
</tr>
<tr>
<td>Education level</td>
<td>11.7 ± 2.8</td>
<td>9.8 ± 2.6</td>
<td>11.3 ± 3.3</td>
</tr>
</tbody>
</table>

Values are means ± SD. *For patients responsive to levodopa, scores are given in the ‘off’ state. †For patients responsive to levodopa, scores are acquired in the ‘on’ state. ‡PSP different from Parkinson’s disease (t-test, P < 0.05); §PSP different from controls and Parkinson’s disease (ANOVA, Bonferroni P < 0.05); †‡PSP different from controls (ANOVA, Bonferroni; P < 0.05). FBI = Frontal Behavioural Inventory (maximum 72); H&Y = Hoehn and Yahr (maximum 5); MMSE = Mini-Mental State Examination (maximum 30); N/A = not applicable; PSP = progressive supranuclear palsy; UPDRS = Unified Parkinson’s Disease Rating Scale (maximum 140, motor maximum 72).
matter segments registered to the standard Montreal Neurological Institute (MNI) stereotactic space were smoothed with an 8 mm isotropic Gaussian kernel, then averaged across subjects to create the grey matter template. Grey matter segments of raw images were registered to the new grey matter template in order to derive normalization parameters to be applied subsequently to the raw images themselves. The volume change effected by normalization was defined as the determinant of the Jacobian matrix specifying the deformation field at each voxel. After misclassified extra-cerebral tissue had been eliminated by multiplication with a binary mask, modulated tissue segments of the normalized images were smoothed with a 12 mm kernel.

The variance in voxel data was partitioned between effects of interest and potential confounders using the general linear model framework. A design matrix was constructed in which three columns of ones and zeros indicated the presence or absence of PSP, Parkinson’s disease or control condition across 61 subjects arranged in rows. A column of ones modelled the mean of the data. Age, sex and global voxel intensity were included as mean-corrected nuisance covariates.

For each of the grey, white and CSF tissue segmentations, a vector of parameter estimates was found at every voxel that minimized the sum of squared residuals in the data. Contrasts of parameter estimates was found at every voxel that minimized the intensity were included as mean-corrected nuisance covariates. A design matrix was constructed in which three columns of ones and zeros indicated the presence or absence of PSP, Parkinson’s disease versus controls, PSP versus Parkinson’s disease, and Parkinson’s disease versus control across 61 subjects arranged in rows. A column of ones modelled the mean of the data. Age, sex and global voxel intensity were included as mean-corrected nuisance covariates.

Statistical associations for all analyses were obtained with SPM99 (Wellcome Department of Imaging Neuroscience, London, UK) on a Matlab 6.1 platform (Mathworks, Natick, MA). Clinico-radiological correlations were performed using SPSS for Windows Version 11.0.1 statistical software.

**Results**

**Clinical variables**

PSP and Parkinson’s disease patients exhibited clinical features typical for their respective diagnosis. All 21 PSP cases
had progressive symmetric parkinsonism accompanied by postural instability as well as clinical and electro-oculographic evidence of vertical supranuclear gaze palsy (Vidailhet et al., 1994; Litvan et al., 1996a). All 17 Parkinson’s disease cases had a levodopa-responsive akinetic-rigid syndrome in the absence of gaze palsy at the bedside and on electro-oculography (Vidailhet et al., 1994; Litvan et al., 1996a). Cognitive and behavioural disturbances, as reflected by MMSE and FBI scores, respectively, were more frequent and severe in PSP than in Parkinson’s disease (see Table 1). The most common abnormal behaviours identified in both disorders were logopaenia and apathy, each occurring in >90% of participants with PSP, and between 38 and 44% of patients with Parkinson’s disease. In contrast, disinhibited type behaviours were infrequent in both PSP and Parkinson’s disease.

**Effects of clinical diagnosis on tissue volumes**

A similar distribution of volume loss in the frontal cortex, subcortical nuclei and periventricular white matter was identified in PSP, whether compared with Parkinson’s disease or controls. Grey and white matter volume loss in PSP relative to controls is illustrated in Figs 1 and 2, respectively. Volume changes are rendered on the mean of normalized tissue segments from the control subjects. Table 2 summarizes local maxima for the main effect of disease condition.

**Parkinson’s disease**

The only region with significant tissue loss in Parkinson’s disease patients relative to controls occurred in the grey matter surrounding the left intraparietal sulcus (Table 2). There were no other differences in volume in Parkinson’s disease patients relative to controls.

**Progressive supranuclear palsy**

Comparing grey matter volumes in PSP versus controls, subcortical tissue loss in PSP was symmetrically distributed in the midbrain, the caudate nuclei, the thalamus, the hypothalamus and, to a lesser extent, the flocculo-nodular lobe of the cerebellum. Atrophy within these structures was maximal in the rostro-dorsal midbrain (area incorporating the superior colliculus, posterior commissure and habenular nuclei), both heads of caudate and the medio-dorsal thalamus (including the latero-dorsal thalamus and extending posteriorly to include the body of the fornix).

Cortical grey matter atrophy in PSP was symmetrical and confined to the frontal cortex, with greatest tissue loss within the inferior frontal gyrus and the mesial frontal cortex. Atrophy within the inferior frontal gyrus was maximal in the orbitofrontal cortex surrounding the horizontal ramus of the lateral fissure [Brodmann areas (BAs) 45 and 47], the postero-inferior portion of the pars opercularis that borders the subcentral gyrus (BA 44), and the orbitofrontal grey matter surrounding the inferior frontal sulcus (BAs 8 and 44). Mesial frontal grey matter atrophy was greatest in the motor cingulate (BA 23), and more anteriorly in the paralimbic association cortex (BAs 32 and 24).

White matter atrophy in PSP was centrally located in a symmetrical distribution, with maximal atrophy in the

**Fig. 1** Statistical parametric map of significant grey matter volume loss in PSP relative to controls, rendered on the mean of normalized grey matter images from control subjects. The threshold for display is \( P < 0.005 \) uncorrected, Z-scores are indicated by colour temperature according to the scale. MNI coordinates (mm) of section (A) \( x = -43 \), (B) \( x = -12 \), (C) \( x = 1.5 \), (D) \( y = -34 \), (E) \( y = -4 \), (F) \( y = 14 \), (G) \( y = 55 \), (H) \( z = -15 \), (I) \( z = -1.5 \), (J) \( z = 30 \).
rostro-dorsal midbrain, the mid corpus callosum, and periventricularly surrounding the lateral ventricles. Increases in sulcal and ventricular CSF volumes in PSP corresponded with regional atrophy in adjacent grey and white matter structures.

**Clinico-radiological correlations**

No significant correlations were identified between the sole local maximum of atrophy in Parkinson’s disease, the left intraparietal sulcus and any of the five clinical variables selected for regression analysis. A total of 10 regions of locally maximal atrophy were analysed in PSP. These included three grey matter regions of interest within the subcortex (rostro-dorsal midbrain, head of caudate and medio-dorsal thalamus) and five cortical regions (orbitofrontal cortex surrounding the inferior frontal sulcus, pars opercularis, motor cingulate and paralimbic association cortex) (see Table 2). Two white matter regions of interest, the rostro-dorsal midbrain and mid corpus callosum, were also examined. As there was no systematic laterality of atrophy for any region of interest, only left hemisphere measures were entered into the regression analyses when bilaterally represented brain regions of interest were examined.

Motor disability, as quantified using the UPDRS-motor subscore, correlated with measures of atrophy for the caudate [adjusted $r^2 = 0.18$, $F(1,19) = 5.5$, $\beta = -0.47$, $P = 0.03$] and the motor cingulate cortex [adjusted $r^2 = 0.46$, $F(2,18) = 9.4$, $\beta = -0.41$, $P = 0.02$] in PSP. In contrast, the severity of frontal behavioural disturbance, as measured using the FBI, helped predict grey matter atrophy in the midbrain [adjusted $r^2 = 0.16$, $F(1,19) = 4.9$, $\beta = -0.45$, $P = 0.04$] and the orbitofrontal cortex surrounding the inferior frontal sulcus [adjusted $r^2 = 0.41$, $F(2,18) = 7.8$, $\beta = -0.57$, $P = 0.004$]. Age on testing contributed significantly to the variance in measures for multiple structures in PSP, including the thalamus, pars opercularis, orbitofrontal cortex surrounding the inferior frontal sulcus and the motor cingulate cortex [range: adjusted $r^2 = 0.16$, $F(1,20) = 4.9$, $\beta = -0.45$, $P = 0.04$ for pars opercularis, to adjusted $r^2 = 0.46$, $F(2,18) = 9.4$, $\beta = -0.54$, $P = 0.004$ for motor cingulate]. Neither disease duration nor MMSE scores contributed significantly to the variance of any brain measure. No significant clinico-radiological correlations were identified for the orbitofrontal cortex surrounding the lateral fissure, the paralimbic association cortices or white matter structures in PSP.

Only one significant correlation was identified in controls, with age accounting for 25% of the variance in measures for the motor cingulate [adjusted $r^2 = 0.25$, $F(1,21) = 8.50$, $\beta = -0.54$, $P = 0.008$].

**Discussion**

These results show that degeneration in both subcortical and cortical sites correlates with the severity of symptoms in PSP. While the distribution of frontal cortical grey and white matter atrophy identified here is broadly similar to that described in a recent VBM study of 12 patients with PSP (Brenneis et al., 2004), we also found significant subcortical atrophy consistent with the distribution of pathology described using other techniques (Hauw et al., 1994; Schulz et al., 1999; Henderson et al., 2000; Cordato et al., 2002; Groschel et al., 2004). In the present study, subcortical grey matter atrophy in mid-stage PSP was concentrated in the caudate nuclei, the medio-dorsal thalamus and the midbrain. These three subcortical structures are functionally related, with the latter two thought to exert major regulatory effects on information processing through the caudate (Percheron et al., 1994). The cortical grey matter atrophy in PSP was limited to the frontal cortex, with little change observed in other cortical lobes.

Frontal grey matter atrophy in PSP was maximal in the orbitofrontal and medial frontal cortices, with preservation of the dorsolateral prefrontal cortex. The orbitofrontal and the medial frontal cortices have been strongly implicated in a variety of behavioural disturbances (Cummings, 1993; Adolphs, 2002). Orbitofrontal lesions are associated with personality changes as well as alterations in interest and initiative (Cummings, 1993). The latter deficits are commonly reported in PSP (Litvan et al., 1996b) and were evident in the majority of our PSP cohort (Cordato et al., 2002). Clinical deficits resulting from medial frontal lesions have been less well studied, but are thought to include profound apathy and, in the case of bilateral lesions, akinetic mutism (Cummings, 1993). Correspondingly, apathy was almost universal in PSP.
cases examined in the present study. The substantial bilateral medial frontal lobe atrophy identified in PSP was not, however, accompanied by akinetic mutism in any case.

The severity of behavioural disturbances in mid-stage PSP correlated most strongly with atrophy of the orbitofrontal cortex surrounding the inferior frontal sulcus, although there was also a weaker correlation with midbrain atrophy. This is consistent with the increasingly recognized role played by the midbrain nigrostriatal system in behavioural/cognitive functions (Tzschentke, 2001; Da Cunha et al., 2002; Mura and Feldon, 2003). In addition, the orbitofrontal cortex and midbrain are functionally interconnected through projections from the lateral orbitofrontal circuit (via both the direct and indirect pathways) to the substantia nigra (Cummings, 1993). This interplay of intrinsic frontal cortical and midbrain deficits in PSP contrasts with other related neurodegenerative conditions (e.g. frontotemporal dementia) that similarly display behavioural symptoms but where neurodegeneration is predominantly cortical in distribution (Rosen et al., 2002).

The severity of motor dysfunction in PSP correlated with atrophy of the caudate nucleus and the motor cingulate cortex but not with the midbrain or thalamus. This was despite substantial midbrain and thalamic atrophy in our cases. Functional activity of the motor cingulate is important for appropriate preparation and readiness for voluntary movement (Cunnington et al., 2003) and has been shown previously to correlate with the size of the corpus callosum in normal subjects (Stancak et al., 2003). Consistent with this, we also identified atrophy of the middle anterior segment of the corpus callosum, as previously identified by Yamauchi and colleagues using two-dimensional cross-sectional area measurements of this structure (Yamauchi et al., 1997, 2000).

We also found less substantial deep cerebellar tissue loss in PSP that concentrated in the flocculonodular node. This is consistent with the distribution of cerebellar neurodegeneration reported at post-mortem in PSP (Park et al., 2001; Piao et al., 2002; Tsuboi et al., 2003) and incorporated in the neuropathological diagnostic criteria for this disorder (Hauw et al., 1994). Flocculonodular node involvement in PSP may contribute to the postural instability (via dominant afferent and efferent connections with brainstem vestibular nuclei) and vertical gaze palsy (via connections with the lateral geniculate nucleus, superior colliculi and pontine nuclei) that characterize this disorder (Litvan et al., 1996a; Ghez and Thach, 2000). However, as all PSP patients recruited into the present study were required to exhibit gaze palsy and early postural instability, we were unable to explore correlations between these two hallmark motor features and regional volume measures.

Age on testing correlated with measures for multiple grey matter regions in PSP and with the motor cingulate in controls. A previous VBM study in 465 normal adults demonstrated a linear decline in grey matter with age in cortical regions, including the cingulate, which are the approximate areas found here to correlate with age in PSP (Good et al., 2001). Our study of 66 patients and controls was not comparably powered to detect all age-related effects on brain volumes identified by Good et al. (2001). The absence of an association between disease duration and any of the brain measures in PSP may suggest that regional brain atrophy identified by the present study is a relatively early feature of the disease. This early atrophy may be magnified in elderly PSP patients. Our previous studies suggest that atrophy of other brain regions, including the parietal cortex, occurs in the later stages of the disease in PSP (Cordato et al., 2000, 2002). Further clarification of the progression of atrophy through the disease course requires longitudinal morphometric analyses.

In contrast to the wide distribution of atrophy in PSP, modest grey matter atrophy, insufficient to impact on overall parietal lobar volume, was limited to cortex surrounding the left intraparietal sulcus in Parkinson’s disease. This brain region is thought to play a role in the control of visuospatial attention (Kusunoki et al., 1997). Intraparietal atrophy may contribute to deficits in the voluntary and sustained control of visuospatial attention previously described in Parkinson’s disease (Wright et al., 1993; Yamaguchi and Kobayashi, 1998).

Another recent MRI study of non-demented Parkinson’s disease reported substantial multi-focal right-sided frontal grey matter atrophy (Burton et al., 2004). This apparent discrepancy with our data may be attributable to the older age at disease onset and at testing in this study [mean age at testing 75.2 years, duration of illness 43.5 months (Burton et al., 2004)]. Later onset disease (>65 years; Dubois et al., 1990) and advancing age (Aarsland et al., 2001, 2003) have both been implicated as risk factors for cognitive disturbances, including marked frontal lobe dysfunction, in Parkinson’s disease. Indeed, our previous work suggests that in Lewy body disorders, frontal atrophy at post-mortem (symmetrical in distribution) is only identified in end-stage disease cases satisfying consensus guidelines for dementia with Lewy bodies (McKeith et al., 1996; Cordato et al., 2000).

Overall, despite similar motor deficits to those observed in PSP, our data suggest that little volume loss occurs in levodopa-responsive Parkinson’s disease. The relative lack of atrophy in Parkinson’s disease implies that motor deficits in this disorder relate predominantly to abnormalities caused by the loss of selective dopaminergic (and other neurotransmitter) systems. The more severe and multi-focal nature of structural brain changes detected in PSP compared with Parkinson’s disease are likely to be key contributory factors to the poor responsiveness of PSP to dopaminergic medication.

Some caution must be exercised when interpreting correlation analyses between clinical parameters and VBM data, as the latter are statistical measures of the probability of tissue loss. Nevertheless, our data provide compelling evidence to suggest that intrinsic neurodegeneration of specific subcortical nuclei and subregions of the frontal cortex relate to both the motor and behavioural deficits in PSP and can differentiate this disorder from Parkinson’s disease within 2–4 years of symptom onset. It will be important to determine the
early mechanisms for this marked, selective regional atrophy in PSP if future interventions are to be developed to prevent or at least alleviate this disorder’s debilitating symptomatology.

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References


